SGLT2 inhibitors in the treatment of diabetic nephropathy

KCC staff education

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Disclosures

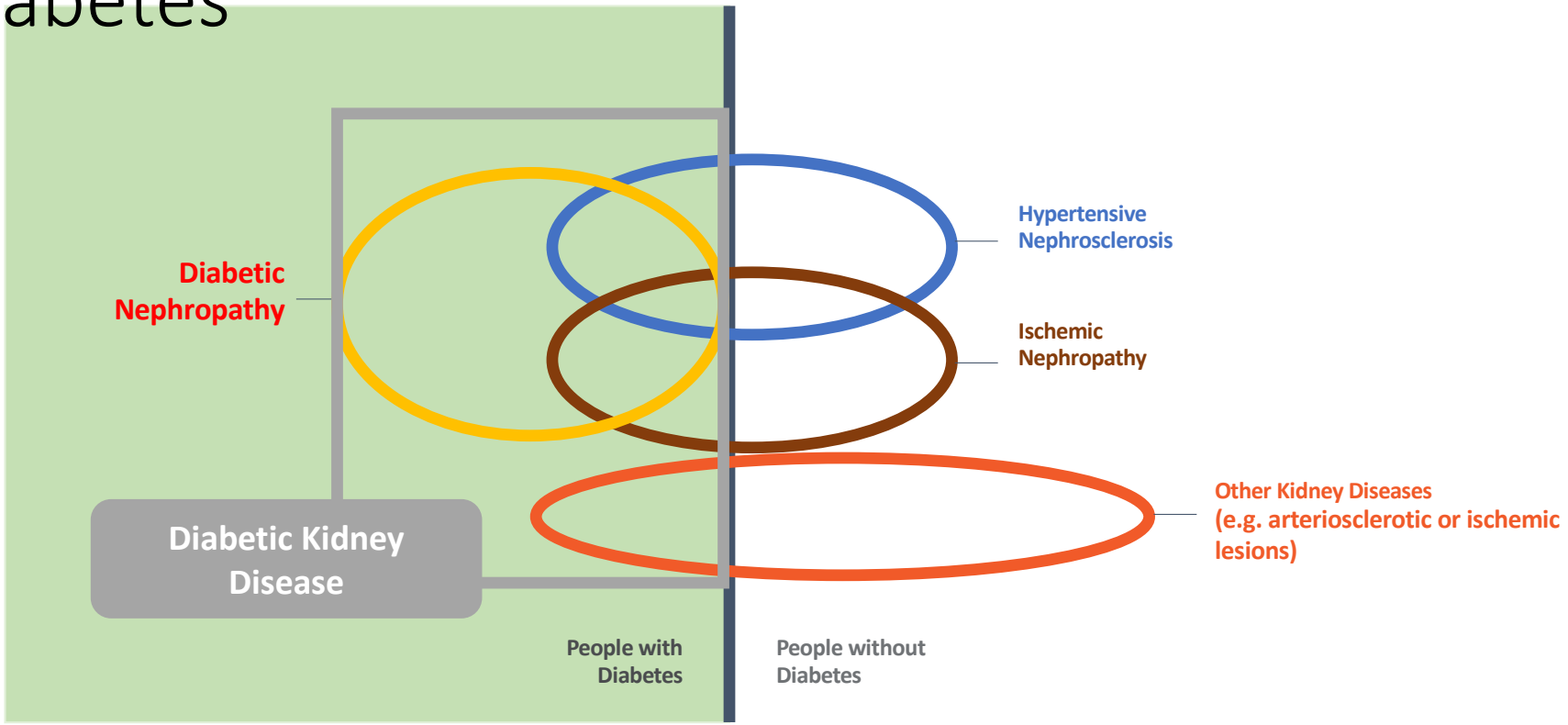
- I have accepted consultant, advisory, speakers honoraria and/or grants from:
  - AstraZeneca Canada
  - Boehringer Ingelheim Canada
  - Janssen Canada
  - Otsuka Pharmaceuticals Canada
  - Sanofi Canada

- Many of these slides/images were created as part of a slide set entitled “Renal Leap” with oversight from Drs. P MacFarlane and J Weinstein. They have been modified for this session

Outline

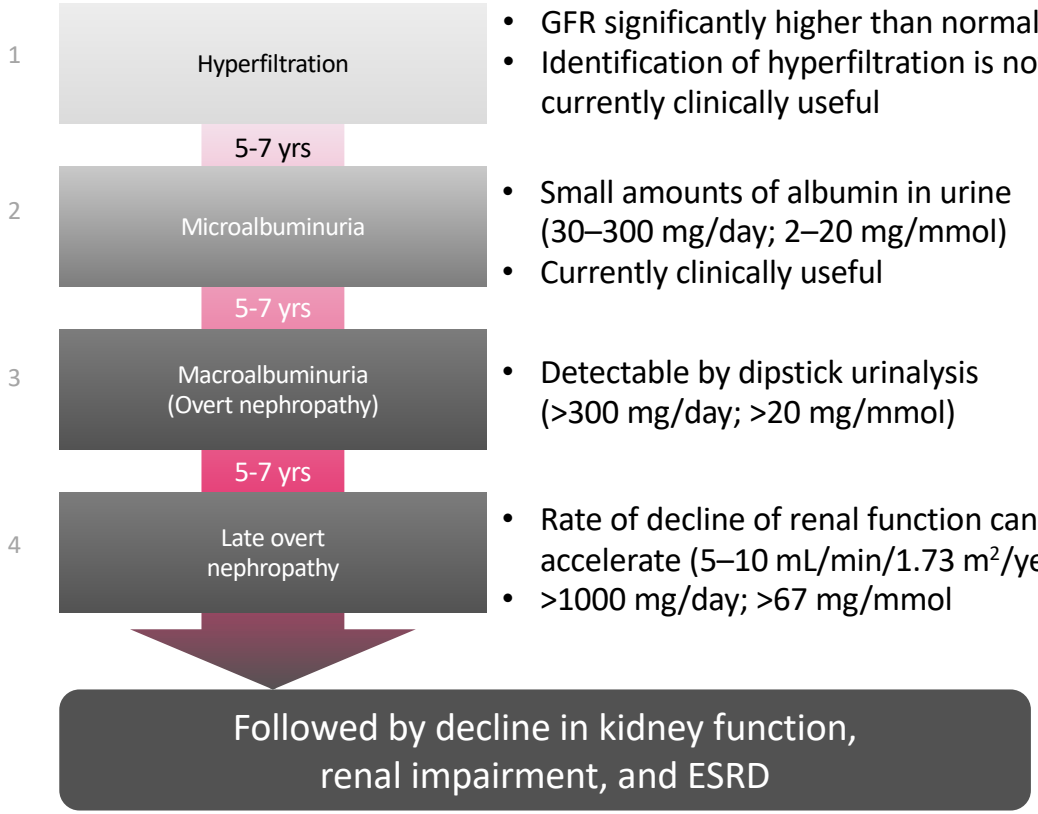
- Overview of diabetic nephropathy and its consequences
- The existing standard of care including RASB
- SGLT2 inhibitors, how they work
- Results of SGLT2 trials including CREDENCE
- Safety and use of SGLT2i in CKD
- Upcoming trials/future landscape of diabetic/CKD treatment

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.

Diabetic Nephropathy



- GFR significantly higher than normal
- Identification of hyperfiltration is not currently clinically useful

- Small amounts of albumin in urine (30–300 mg/day; 2–20 mg/mmol)
- Currently clinically useful

- Detectable by dipstick urinalysis (>300 mg/day; >20 mg/mmol)

- Rate of decline of renal function can accelerate (5–10 mL/min/1.73 m^2/year)
- >1000 mg/day; >67 mg/mmol

- Progression can be accelerated by other comorbidities
- Many people with T2DM do not follow this “classical” progression
  - Over half of patients in United Kingdom Prospective Diabetes Study (UKPDS) cohort who developed eGFRs <60 mL/min/1.73 m^2 showed no preceding albuminuria

ESRD: End-stage renal disease, i.e. progression of kidney disease to failure requiring dialysis or transplant

Thomas et al. *Nat Rev Dis Primers.* 2015;1:15018. doi: 10.1038/nrdp.2015.18; McFarlane et al. *Can J Diabetes*. 2018;42:S201-S209.

DKD prevalence and burden

- **40-50%** of people with diabetes will develop DKD[1,2]
  - **CKD is more common than CVD** in patients with T2DM (24.1% vs 21.6%)[3]
  - Co-prevalence of CKD + CVD rises 6-fold from age <65 years (3.0%) to ≥75 years (18.2%)[3]
- Diabetes is the **leading cause of new cases of ESRD** in Canada[4]
  - **~50%** of adults **requiring dialysis or renal replacement** have ESRD attributable to diabetes[2]
- **DKD can lead to complications**, including significant reductions in both length and quality of life[5]
  - Between 1990 and 2012, number of **deaths due to DKD rose by 94%**[1]
  - This rise is one of the highest observed for all reported chronic diseases

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.

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

(Grade A)

Target ≤ 7.0%

(Grade A)

Target < 130/80 mmHg

(Grade A)

Treatment

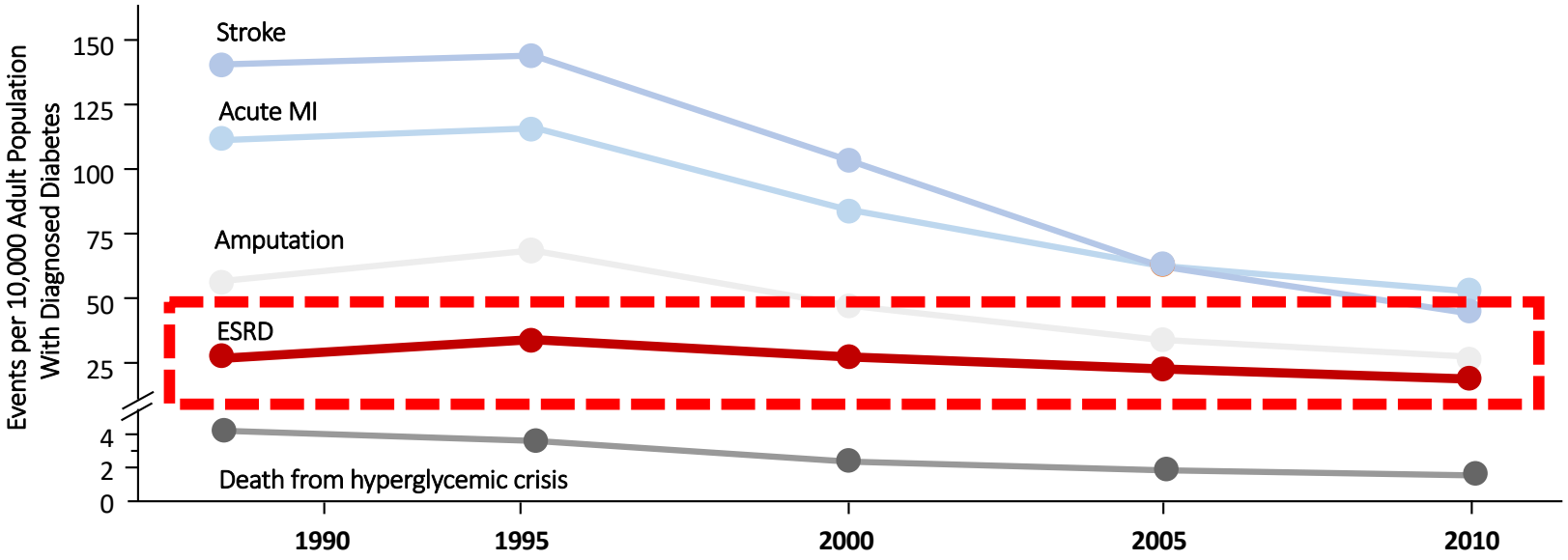
Grade A recommendations are supported by systematic overview or meta-analysis of high-quality randomized clinical trials (RCTs) or appropriately designed RCT(s) with adequate power to answer the question posed by the investigators

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 three strategies, there has been little improvement in the rate of ESRD

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

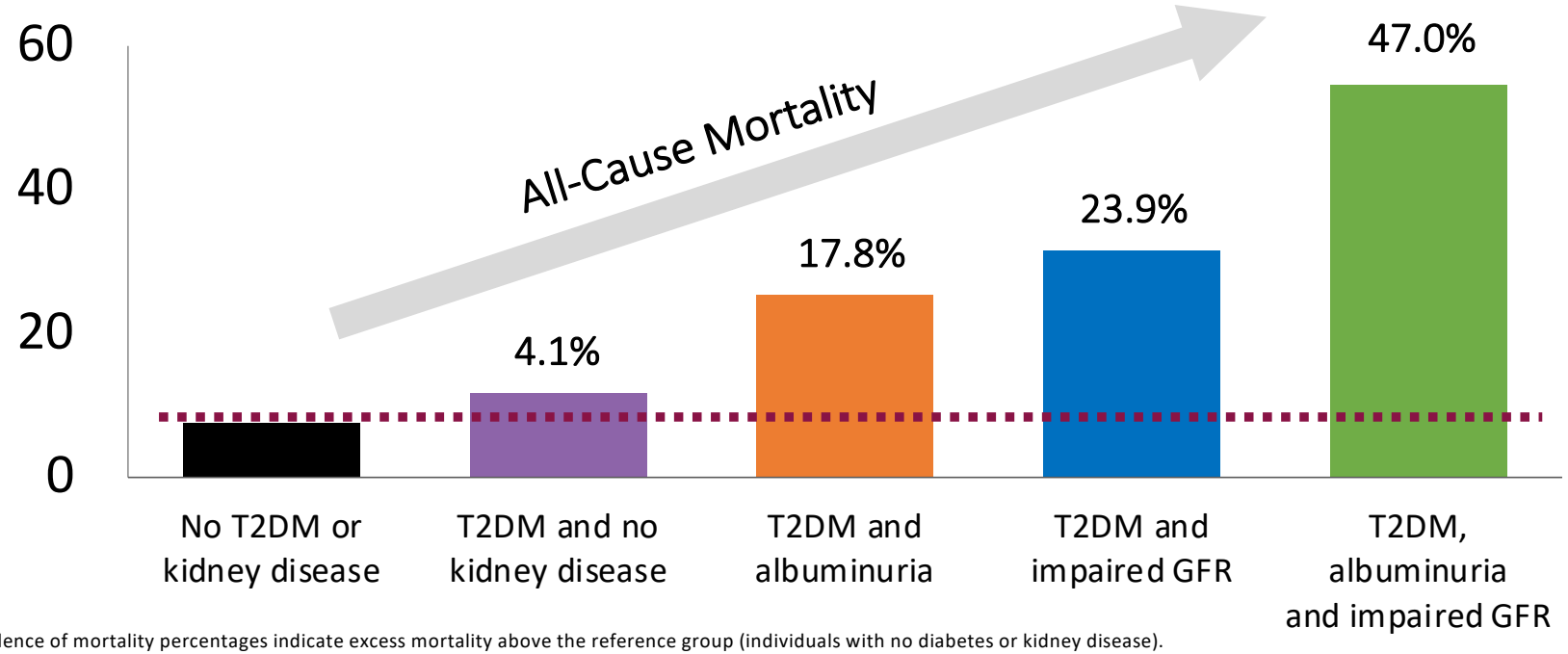


ESRD, end-stage renal disease; MI: myocardial infarction

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

DKD is Associated with Substantial Excess Risk of All-Cause Mortality

Ten-year standardized all-cause mortality by diabetes and kidney disease status (data from US NHANES III)



Incidence of mortality percentages indicate excess mortality above the reference group (individuals with no diabetes or kidney disease).
US, United States; NHANES III: Third National Health and Nutrition Examination Survey; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; Cr, creatinine.
Study included 15,046 participants aged ≥20 years who participated in a health examination and had available data on medications used, serum Cr and urine albumin and Cr concentrations and follow-up mortality data through 2006. Kidney disease was defined as urinary ACR ≥30 mg/g (≥3.4 mg/mmol) and/or eGFR <60 mL/min/1.73 m^2

Afkarian M et al. *J Am Soc Nephrol*. 2013 Feb;24(2):302-8.

Evidence behind ACEi or ARB: "Gold Standard" for DKD

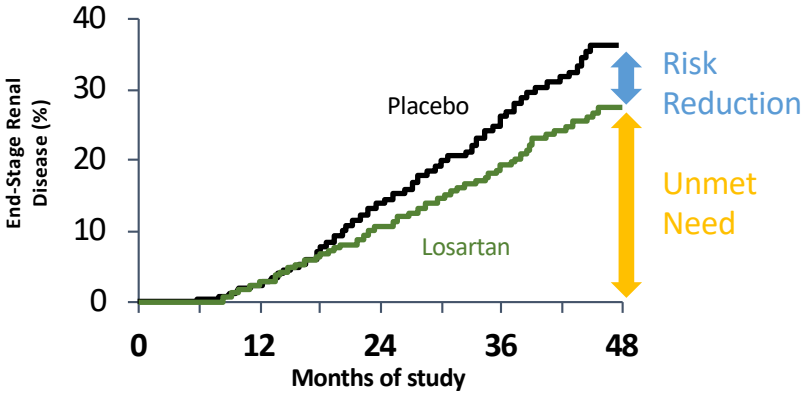
	Albuminuria	Baseline renal function	2xCr, ESRD, Renal Death – # of events	Relative Risk Reduction
IDNT[1] **(irbesartan)**	Median 1900 mg/d (1000 – 3800 mg/d)	Mean Cr: 148 µmol/L	644	20% (p=0.006)
RENAAL[2] **(losartan)**	Median ACR: ~1250	Mean Cr: 168 µmol/L	686	16% (p = 0.02)
ACEi Collaborative study group[3] (captopril)	Mean proteinuria: 2500 mg/d	**Mean Cr: 115 µmol/L**	2xCrR: 68 Death or ESRD: 65	43% (p = 0.007) 46%

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

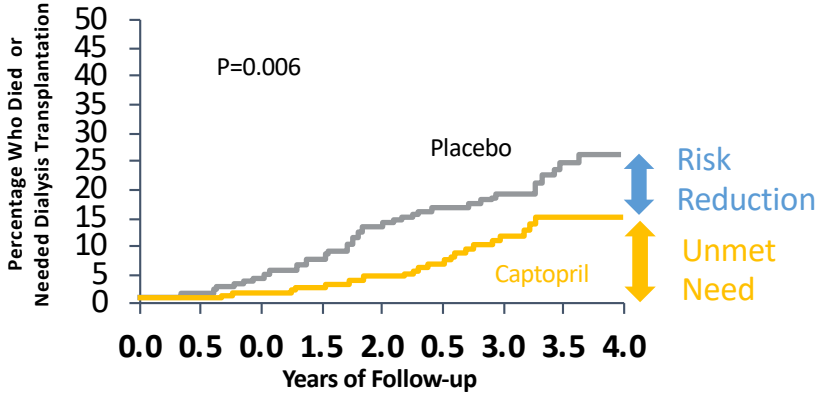
1. Lewis EJ, et al. *N Engl J Med* 2001;345:851-60. 2. Brenner BM et al *New Engl J Med* 2001;345:861-69. 3. Lewis EJ, et al. *N Engl J Med* 1993; 329:1456-1462

ACEi or ARB: "Gold Standard" for DKD

ARB[1]



ACE Inhibitor[2]

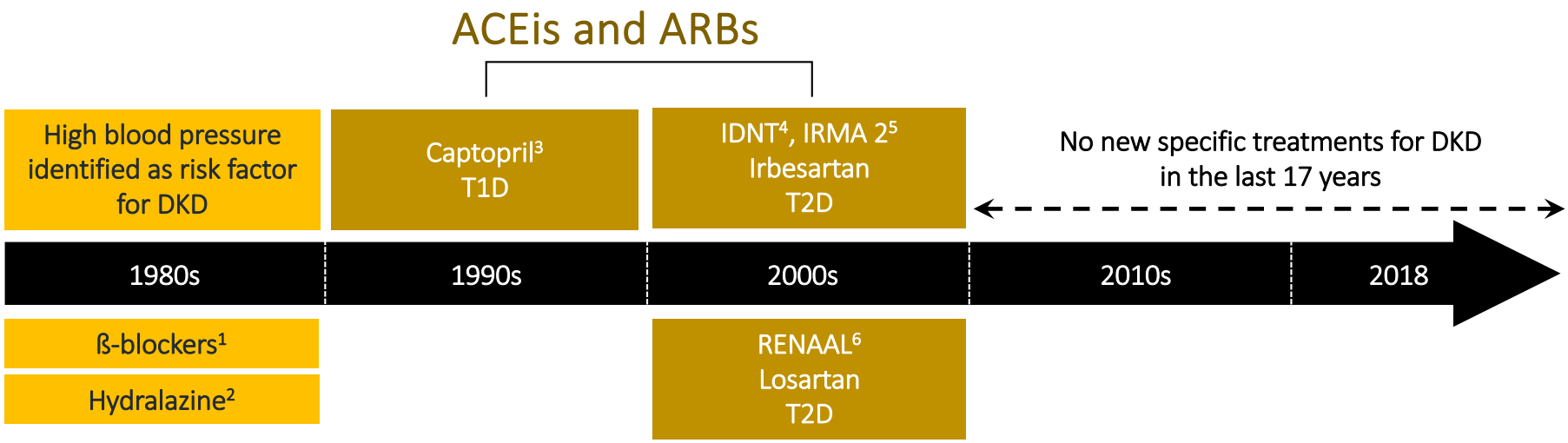


- Risk reduction associated with ACEi or ARB agents was an important development in primary care
- **There is still a clear unmet need for new therapeutic interventions to improve the poor outcomes experienced in DKD**

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

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 DKD since the advent of ACEi or ARB 17 years ago



DKD, diabetic 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].

Emerging evidence for a new intervention in DKD: SGLT2 inhibitors (SGLT2i)

A1C Control

SGLT2i agents effectively lower A1C

BP Control

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

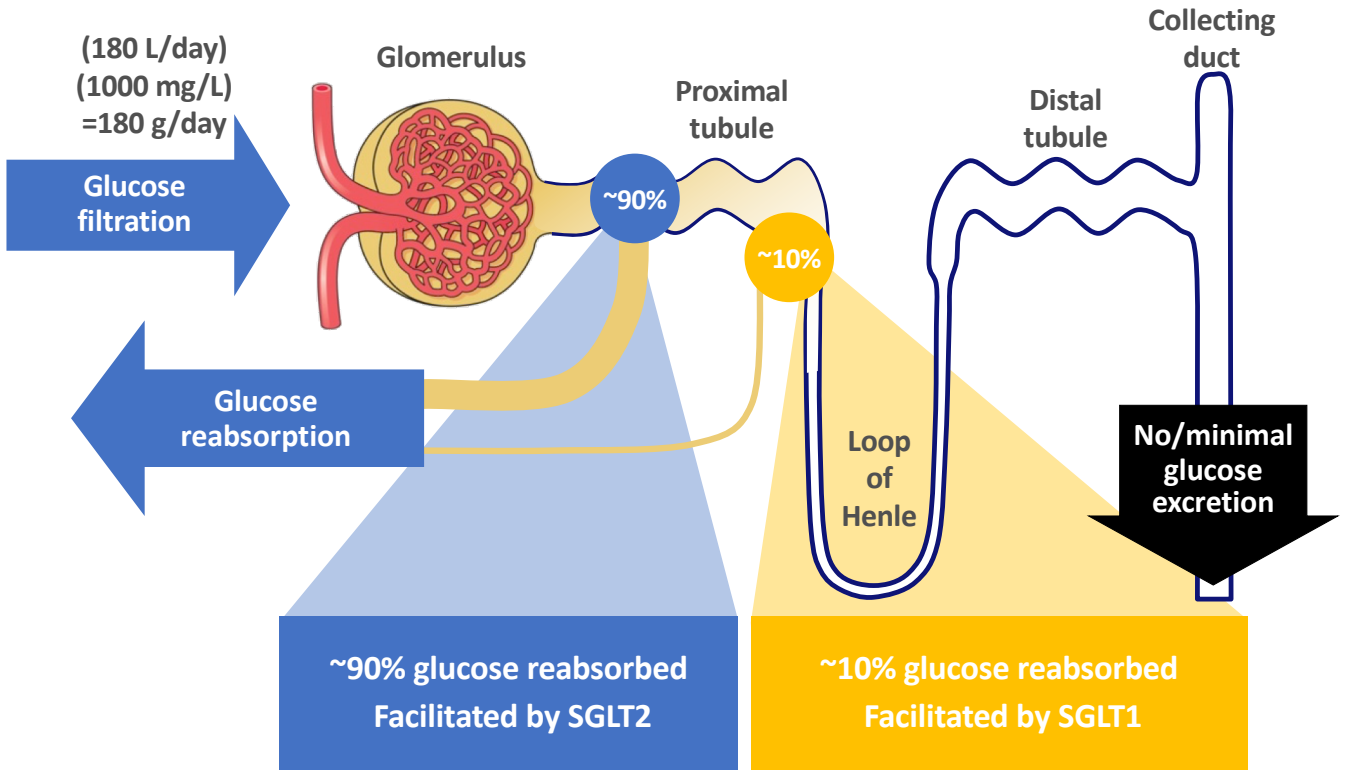
"In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73m^2, an SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy."

– **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.

The Normal Kidney

Renal handling of glucose in non-diabetic individuals

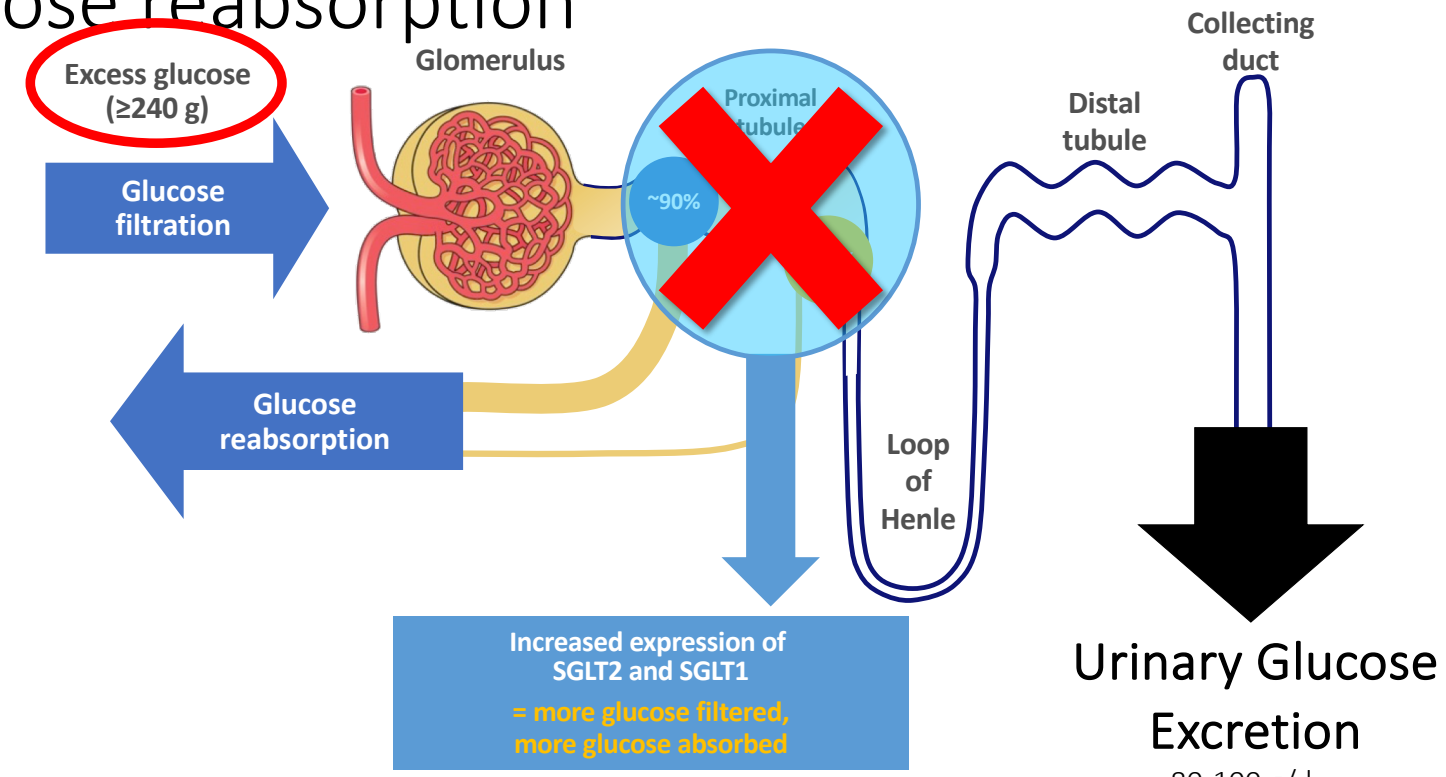


SGLT = sodium glucose cotransporter

Adapted from: 1. Bailey CJ. *Trends Pharmacol Sci* 2011;32:63-71. 2. Chao EC. *Core Evidence* 2012;7:21-28.

The Maladaptive Kidney

Renal handling of glucose in T2DM: increased glucose reabsorption



SGLT = sodium glucose cotransporter

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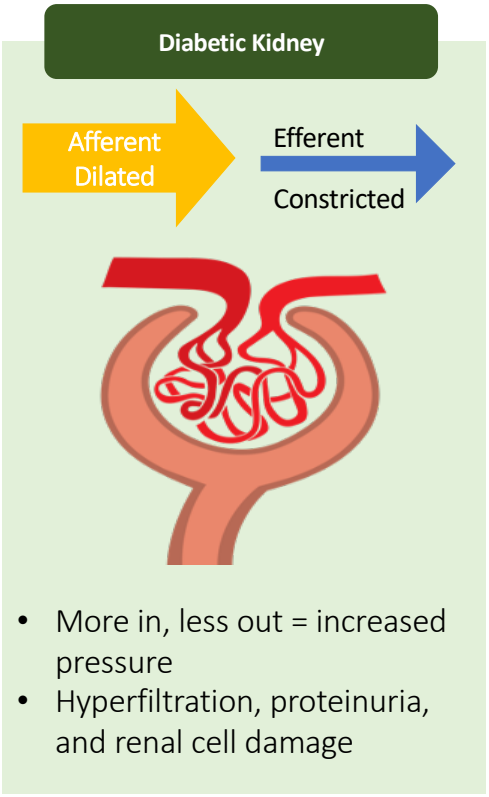
Effect of ACEi and ARBs on intraglomerular pressure

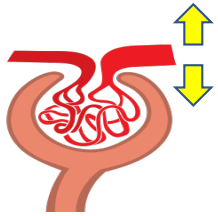


- More in, less out = increased pressure
- Hyperfiltration, proteinuria, and renal cell damage

Pharmacological actions:

ACEi or ARB

Efferent dilation



Hemodynamic effects and clinical implications:

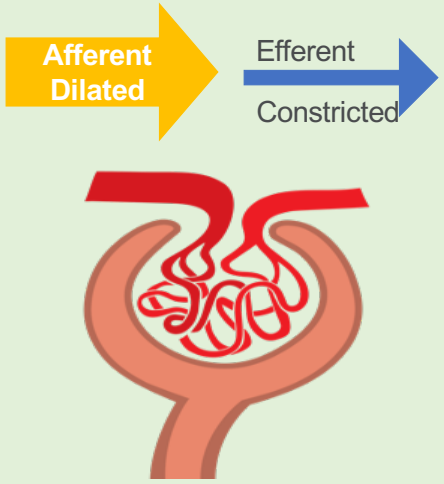
- More out = decreased pressure
- Decreased hyperfiltration
- Proven renal protection in clinical trials

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration

Adapted from: Skrtić M, et al. *Diabetologia* 2014;57:2599–602.

Effect of SGLT2i on intraglomerular pressure

Diabetic Kidney

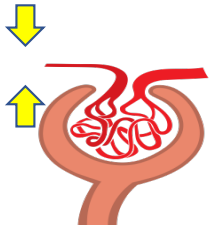


- More in, less out = increased pressure
- Hyperfiltration, proteinuria, and renal cell damage

Pharmacological actions:

SGLT2 inhibition

Afferent constriction



Hemodynamic effects and clinical implications:

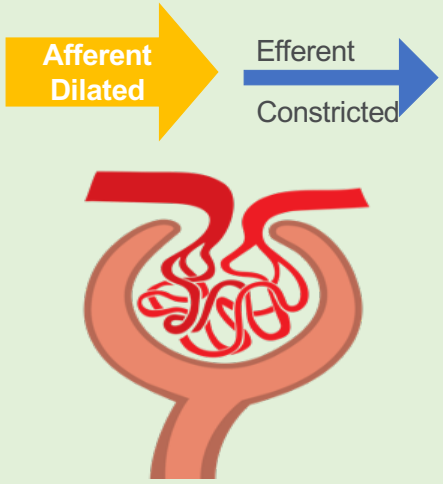
- Less in = decreased pressure
- Decreased hyperfiltration

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration

Adapted from: Skrtić M, et al. *Diabetologia* 2014;57:2599–602.

Effect of SGLT2 inhibition and ACEi and ARBs on intraglomerular pressure

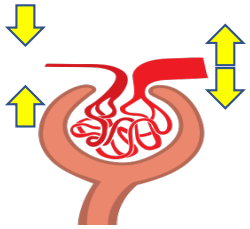
Diabetic Kidney



- More in, less out = increased pressure
- Hyperfiltration, proteinuria, and renal cell damage

Pharmacological actions:

SGLT2 inhibition + ACEi or ARB



Hemodynamic effects and clinical implications:

- Potential for additive effect?
- Potential for long-term renal protection?

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration

Adapted from: Skrtić M, et al. *Diabetologia* 2014;57:2599–602.

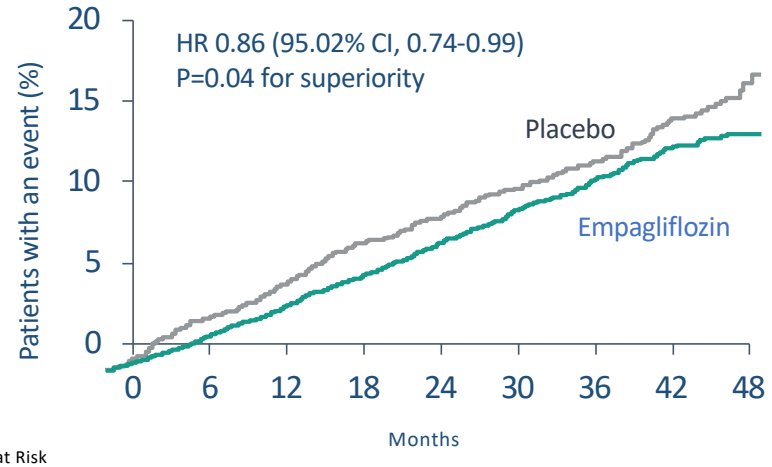
SGLT2 Inhibition

Exploratory data on Renal Efficacy & Safety from Large Cardiovascular Trials

CV Outcomes: EMPA-REG OUTCOME and LEADER

EMPA-REG OUTCOME[1]

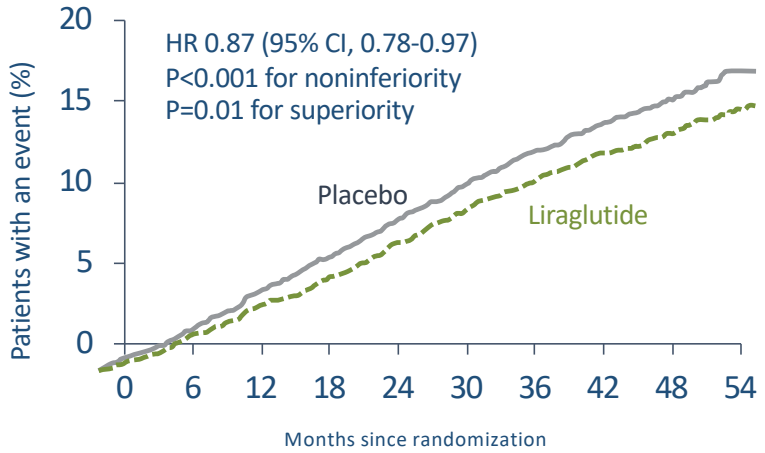
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke



No. at Risk									
	2333	2256	2194	2112	1875	1380	1161	741	166
EMPA	4687	4580	4455	4328	3851	2821	2359	1534	370

LEADER[2]

Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke



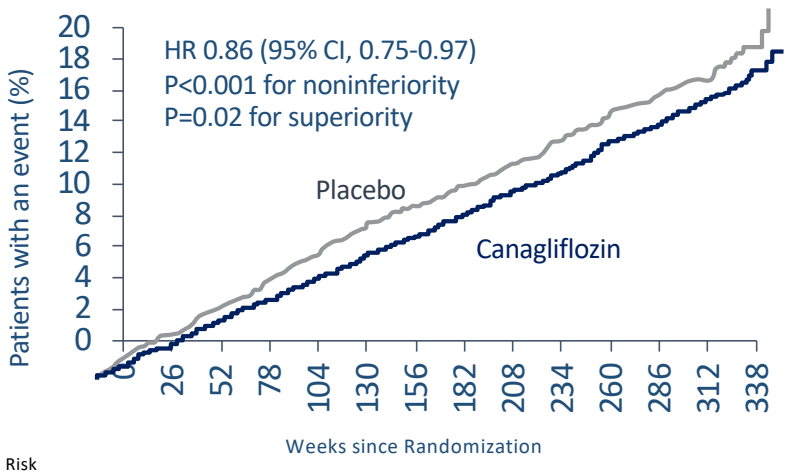
No. at Risk										
	4668	4593	4496	4400	4280	4127	4072	3982	1562	424
LIRA	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

1. Zinman B, et al. *N Engl J Med* 2015;373:2117-28.
2. Marso SP et al. *N Engl J Med* 2016;375:311-22.

CV Outcomes: CANVAS and DECLARE-TIMI 58

CANVAS[1]

Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

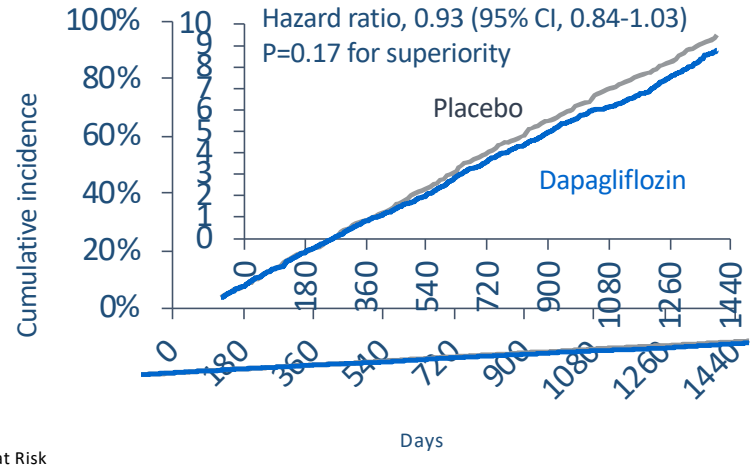


No. at Risk

	4374	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
CANA	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

DECLARE-TIMI 58[2]

Composite of death from cardiovascular death, myocardial infarction, or ischemic stroke



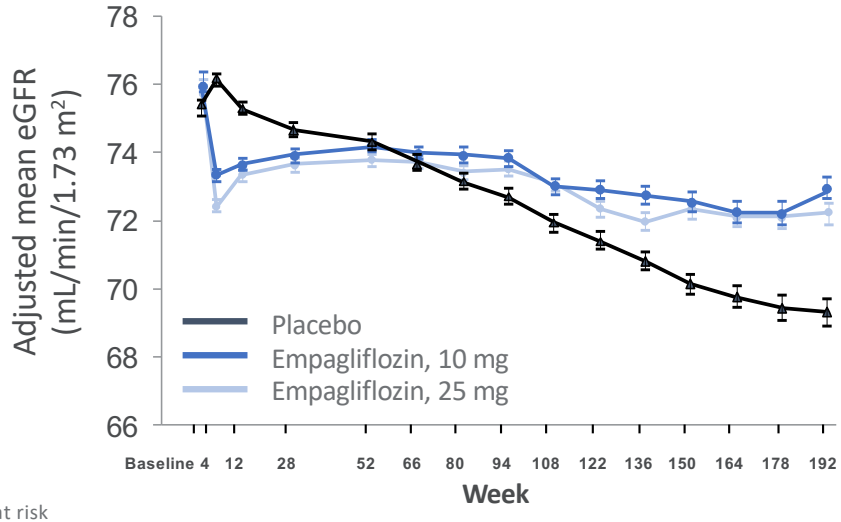
No. at Risk

	8578	8433	8281	8129	7969	7805	7649	7137	5158
DAPA	8582	8366	8303	8166	8017	7873	7708	7237	5225

1. Neal B, et al. *N Engl J Med* 2017;377:644-57.
2. Wiviott SD et al. *N Engl J Med* 2018; DOI: 10.1056/NEJMoa1812389

In CV trials, eGFR initially drops and is stabilized over time

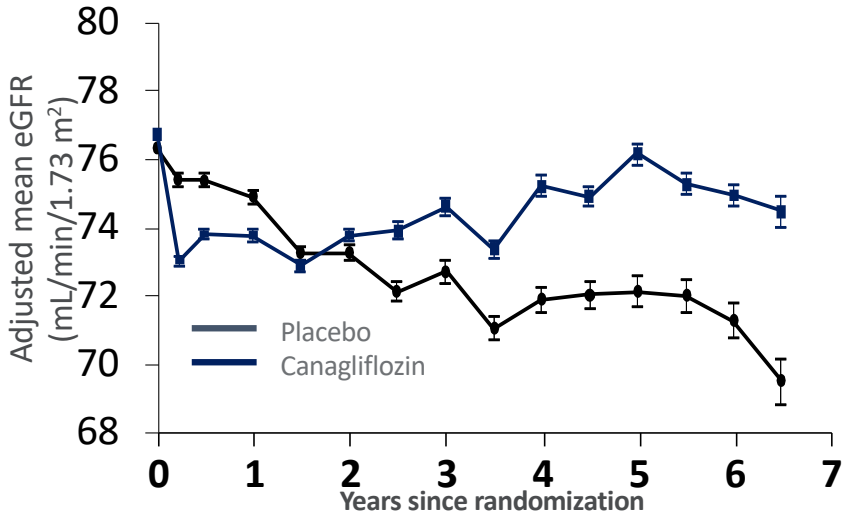
EMPA-REG OUTCOME
Change in eGFR* over 192 weeks[1]



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

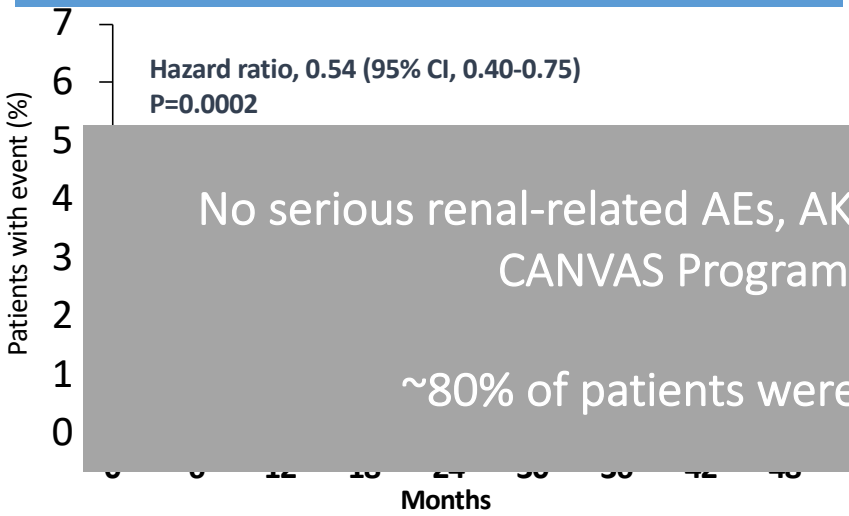
	4276	3867	3212	1030	899	809	694
CANA	5711	5212	4570	2230	2039	1895	1653

*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

In CV trials, SGLT2 inhibitors reduced the exploratory composite renal endpoints by ~45%

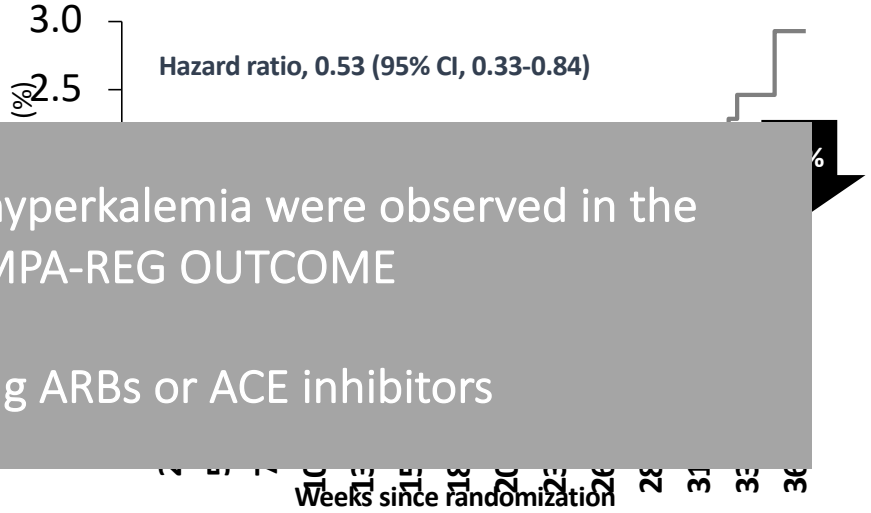
EMPA-REG OUTCOME[1]:
(composite of doubling of SCr*, initiation of renal replacement therapy, or renal death)



No. of patients

	4645	4500	4377	4241	3729	2715	2280	1496	360
EMPA	2323	2229	2146	2047	1771	1289	1079	680	144

CANVAS Program[2]
(composite of doubling of SCr, ESRD, or renal death)



No. at risk

	4347	4291	4235	4170	3050	1693	1294	1276	1253	1229	1200	1181	844	237
CANA	5795	5741	5677	5599	4476	3089	2670	2641	2597	2564	2520	2481	1809	501

No serious renal-related AEs, AKI, or hyperkalemia were observed in the CANVAS Program or EMPA-REG OUTCOME

~80% of patients were taking ARBs or ACE inhibitors

* Accompanied by eGFR ≤ 45 mL/min/1.73 m^2. Kaplan- Meier estimate. Treated set.

CANA: canagliflozin; SCr: serum creatinine; ESRD: end-stage kidney disease; PBO: placebo; HR: hazard ratio; CI: confidence interval

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

Putting DKD evidence into perspective

	Albuminuria	Baseline renal function	2xCr, ESRD, Renal Death # of events	Relative risk reduction
IDNT[1]	Median 1900 mg/d (1000 – 3800 mg/d)	Mean Cr: 148 µmol/L	644	20%
RE				
AC				
CA (80				
EM (81				
DECLARE-TIMI-58[9,10] (81% on RAASi)	<30 mg/g: 68% 30–300 mg/g: ~23.4% >300: ~6.8%	Mean eGFR: 86 mL/min/1.73 m^2 eGFR<60=9.1%	≥40% ↓ in GFR, ESRD, renal death: 365	47%

RAAS blockade trials were dedicated renal trials consisting of patients with advanced DKD and included primary renal endpoints.

CANVAS, EMPA-REG, and DECLARE-TIMI 58 were CVOTs consisting of patients with mild or no DKD and included exploratory or secondary renal outcomes.

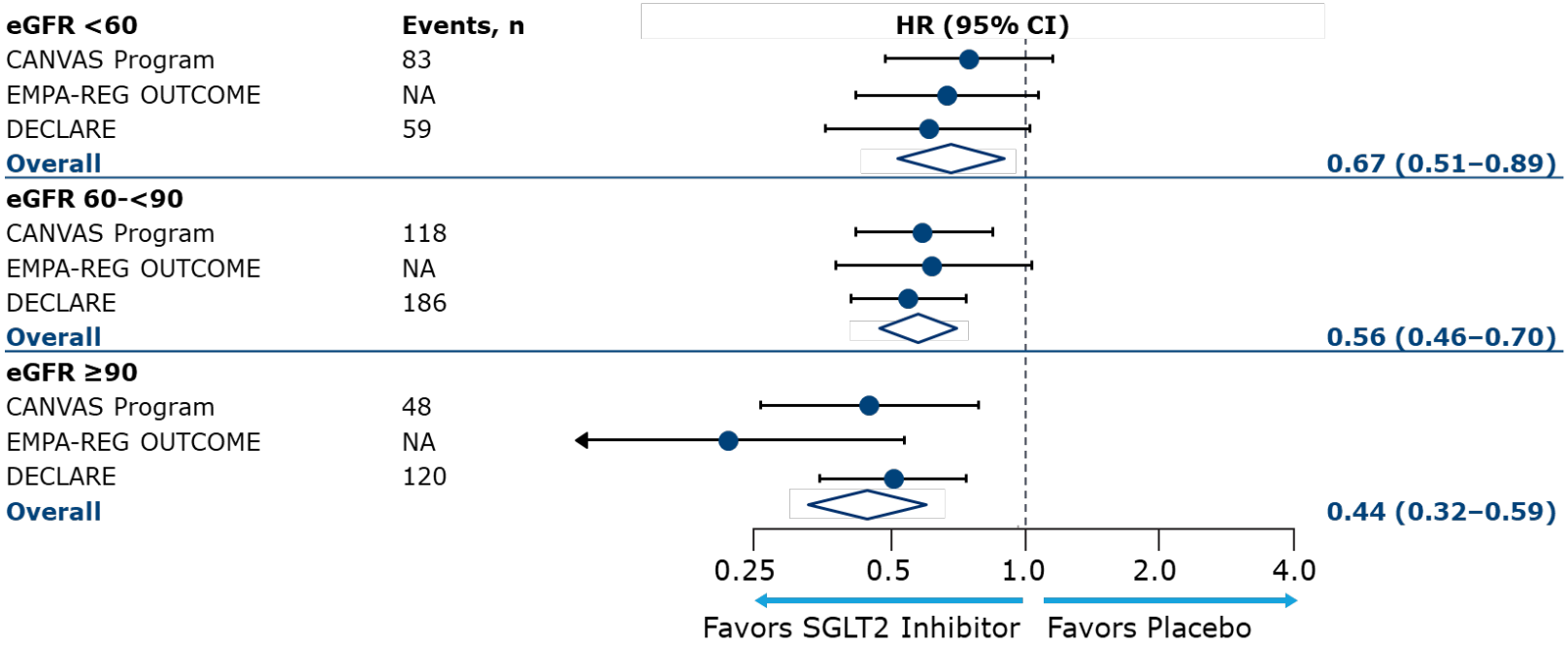
***Kidney outcomes were not confirmed or adjudicated during the EMPA-REG OUTCOME trial[5]**

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. Neal B, et al. *N Engl J Med*. 2017;377:644-57. 5. Perkovic V, et al. Presented at ASN Kidney Week 2017 Annual Meeting; October 31 – November 5, 2017; New Orleans, Louisiana.
6. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691-704. 7. Zinman B, et al. *N Engl J Med* 2015;373:2117-28. 8. Wanner C et al. *N Engl J Med* 2016;375:323-34.
9. Raz I, et al. Diabetes Obes Metab. 2018;20:1102–1110. 10. Wiviott SD, et al. *N Engl J Med* 2018; DOI: 10.1056/NEJMoa1812389.

Landscape prior to CREDENCE

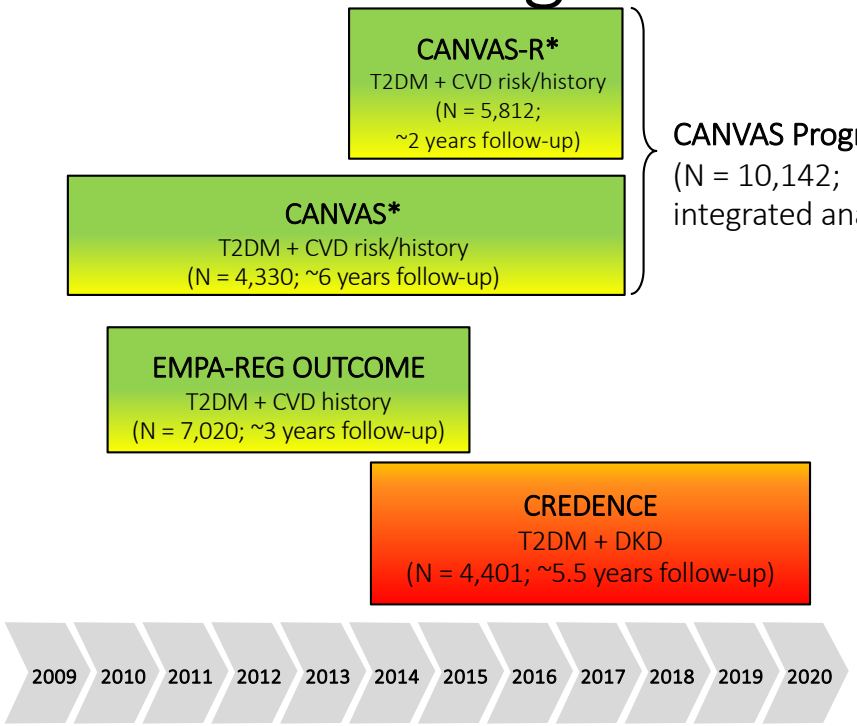
CV outcomes trial results suggested possible attenuation of renal effects in patients with reduced kidney function

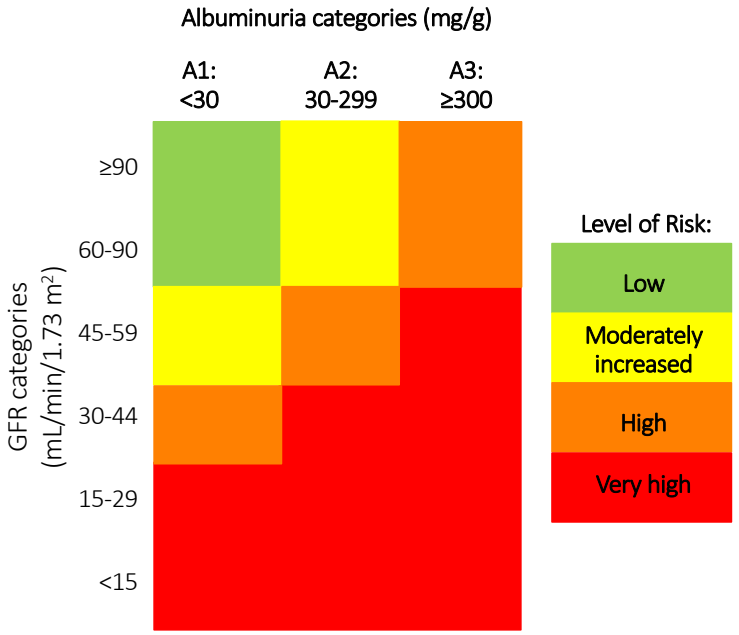
Composite of worsening of renal function, ESKD, or renal death



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

CREDENCE was designed specifically for renal outcomes in a higher risk renal population





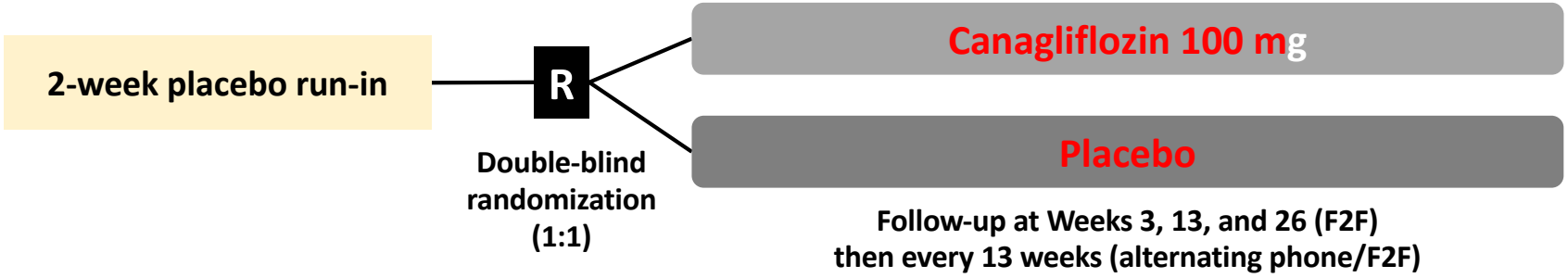
*Note that the patient populations in CANVAS and CANVAS-R are nearly identical to facilitate an integrated analysis of the data.

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

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



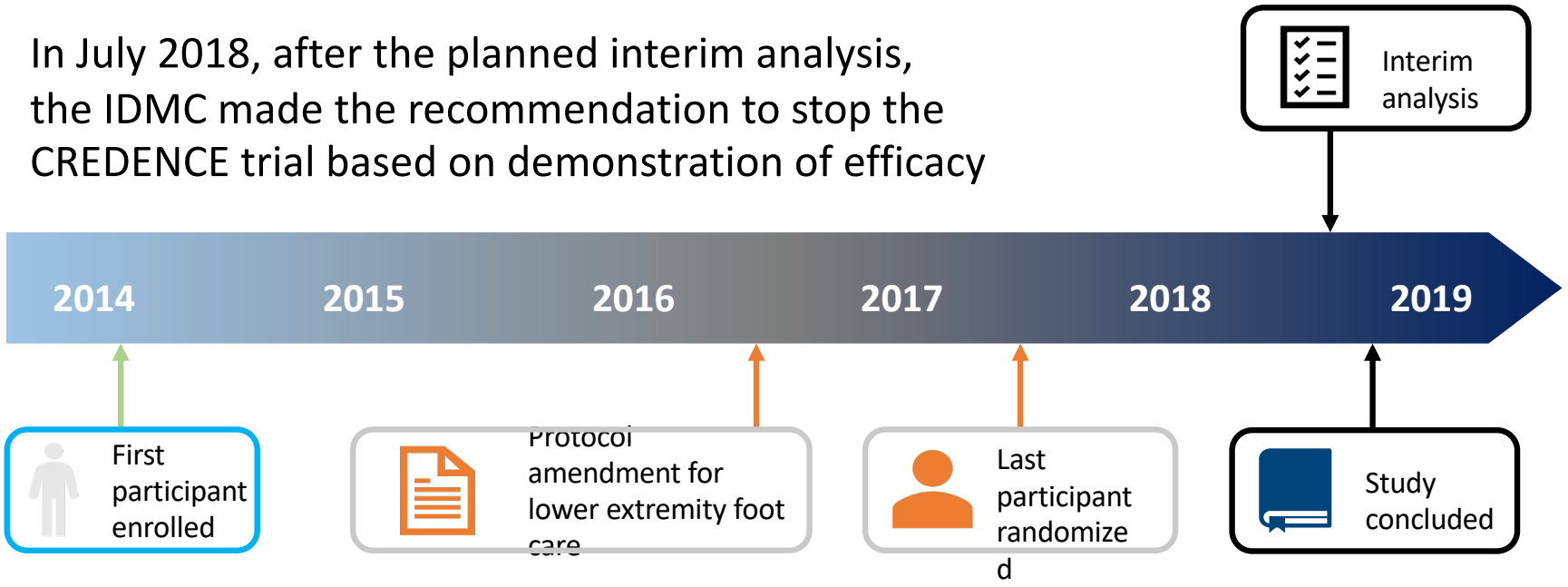
Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

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.

Study Timeline

In July 2018, after the planned interim analysis, the IDMC made the recommendation to stop the CREDENCE trial based on demonstration of efficacy



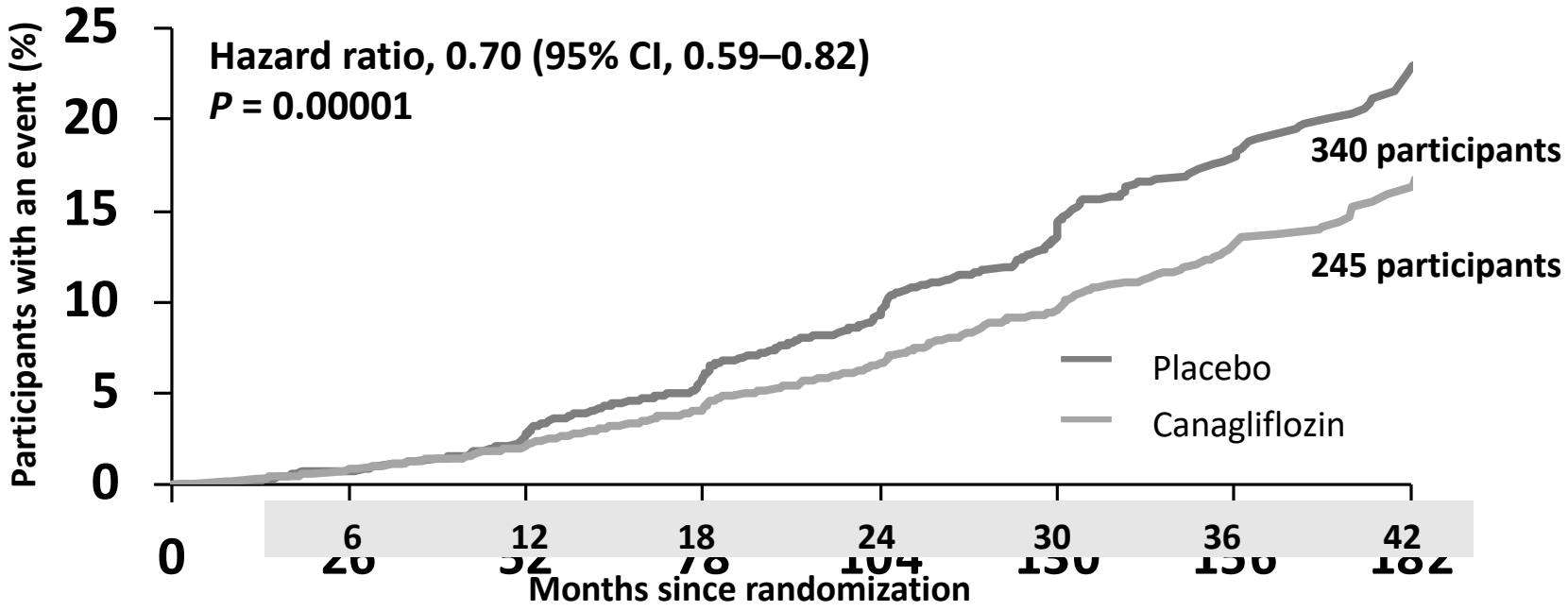
CREDENCE: Key baseline characteristics

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

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.

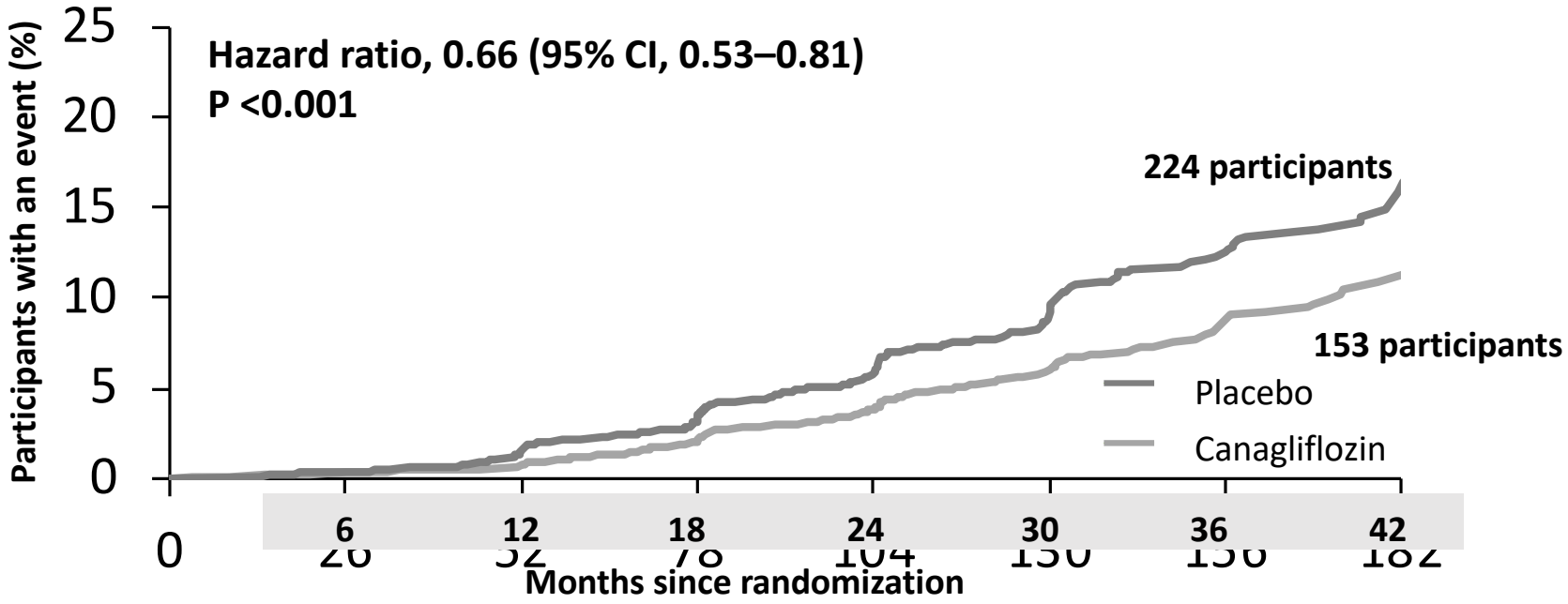
Primary Endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death



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.

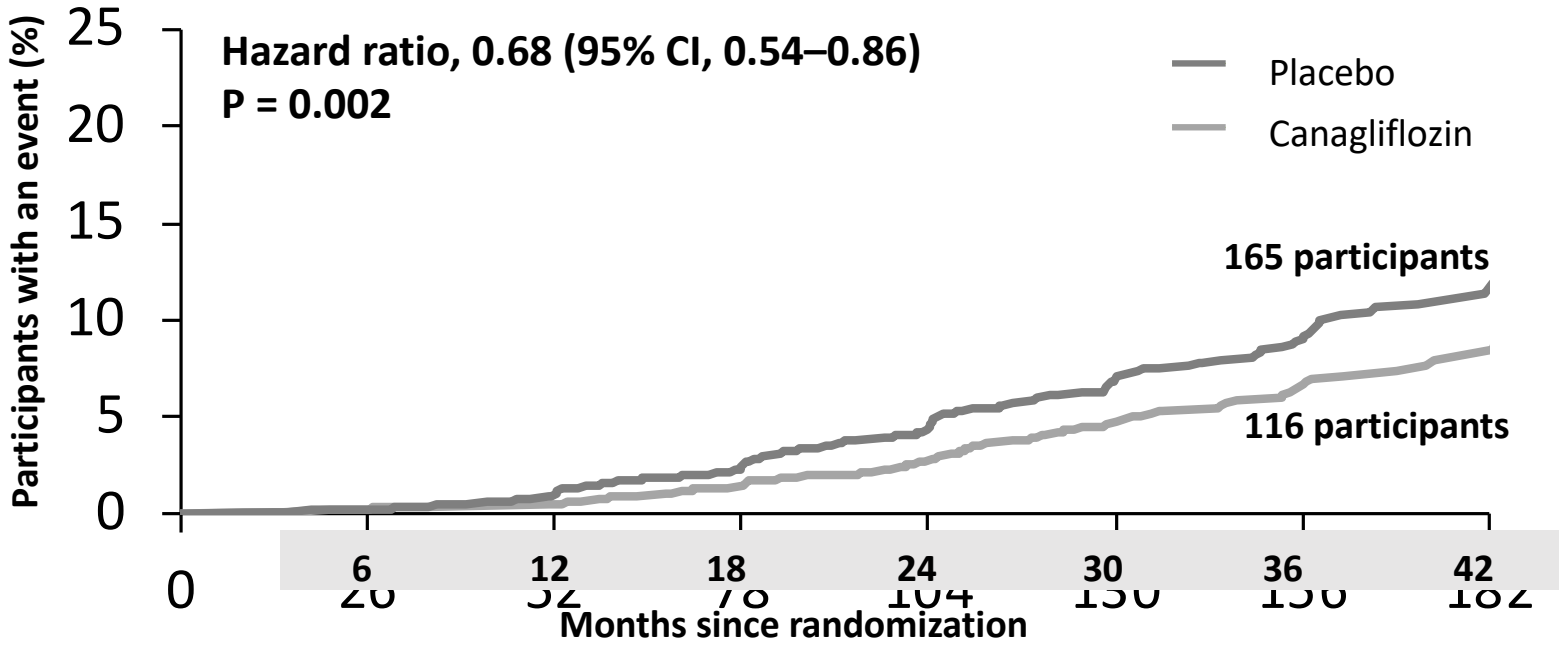
Secondary Endpoint: Composite of ESKD, doubling of serum creatinine, or renal death



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.

Secondary Endpoint: End-stage kidney disease

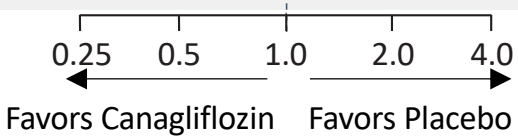


No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

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

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 m^2	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)	–

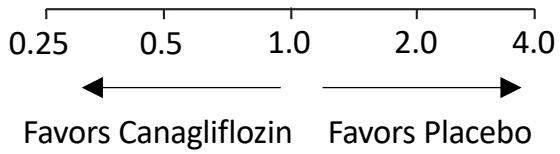


* Post-hoc analysis

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

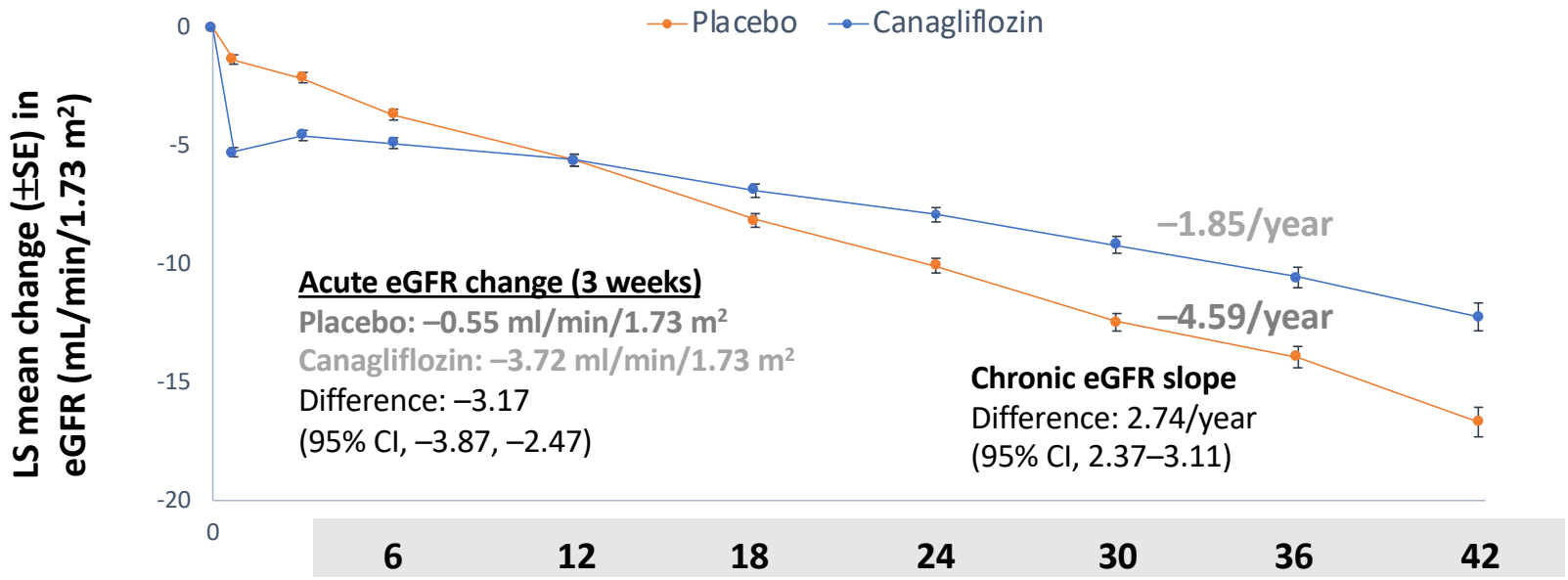
Primary outcome by screening eGFR and albuminuria

	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
≤1000 mg/g		0.76 (0.55–1.04)	
>1000 mg/g		0.67 (0.55–0.81)	



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

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.

Summary: Renal outcomes

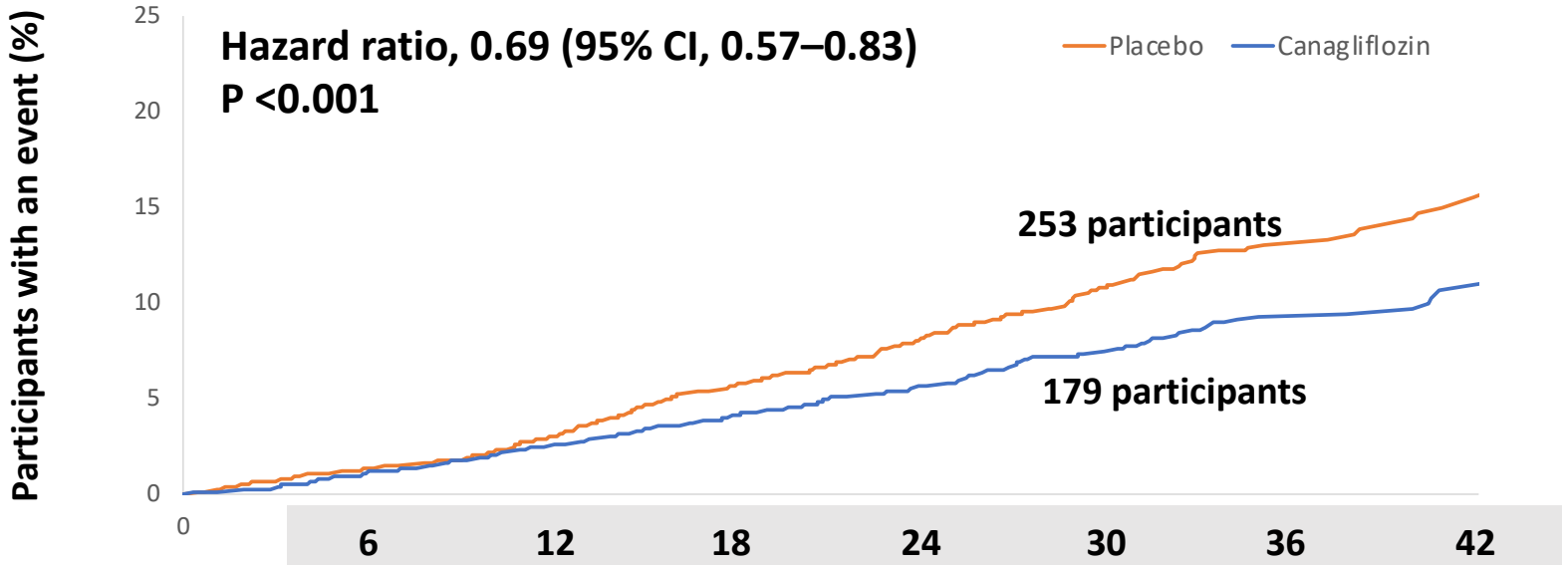
- Canagliflozin **reduced the risk of the primary outcome** of ESKD, doubling of serum creatinine, or renal or CV death **by 30%** (P = 0.00001)
  - The results were consistent across a broad range of prespecified subgroups
- Canagliflozin also **reduced the risk of the secondary outcome** of ESKD, doubling 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**
- There is an expected initial drop in GFR
- Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m^2/year (–1.9 vs –4.6)

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.

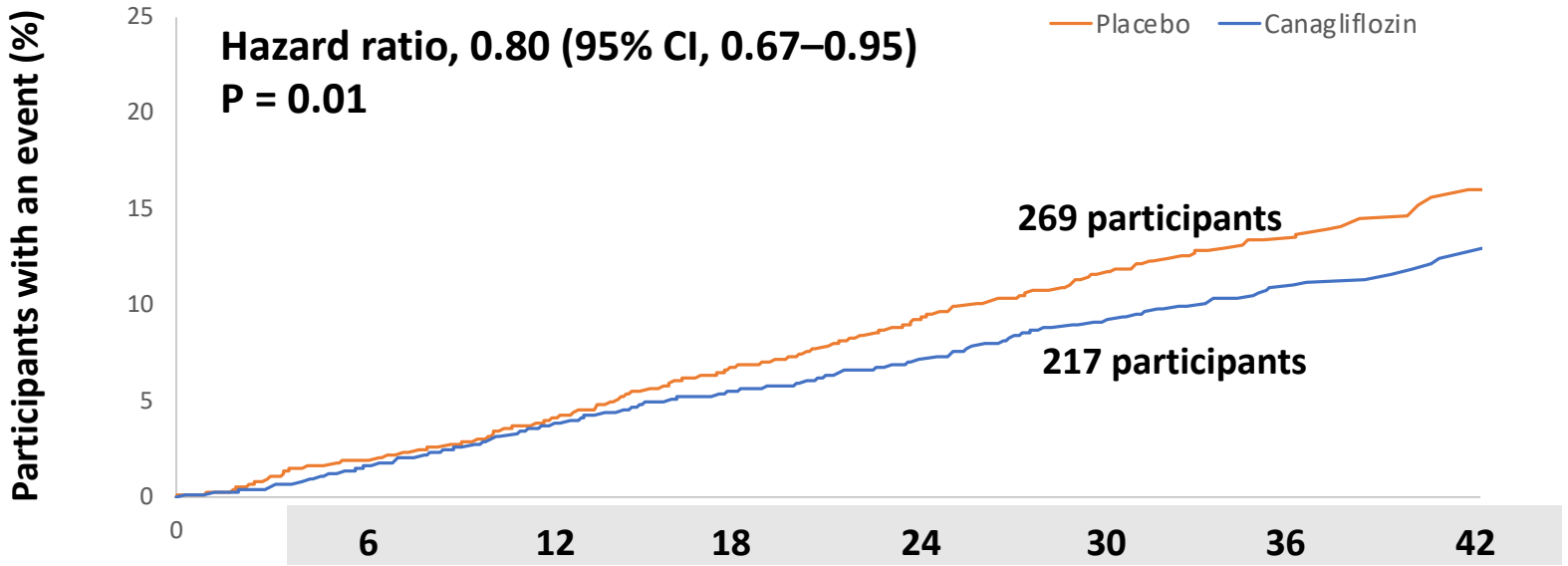
Secondary Endpoint: CV death or hospitalization for heart failure



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)



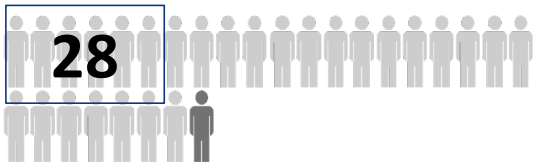
No. at risk								
Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

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

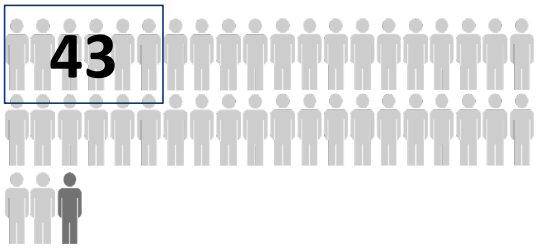
NNT for renal and CV outcomes over 2.5 years

Primary composite outcome

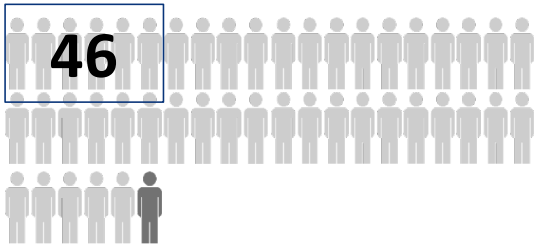
ESKD, doubling of serum creatinine, or renal death



ESKD



Hospitalization for heart failure

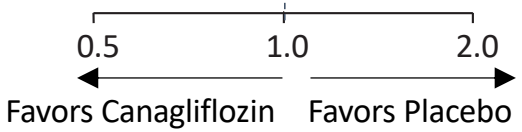


CV death, MI, or stroke

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

Safety: 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)

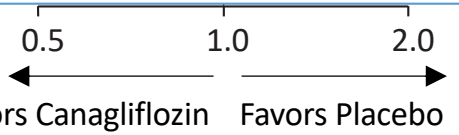


Includes all treated participants through 30 days after last dose.

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)

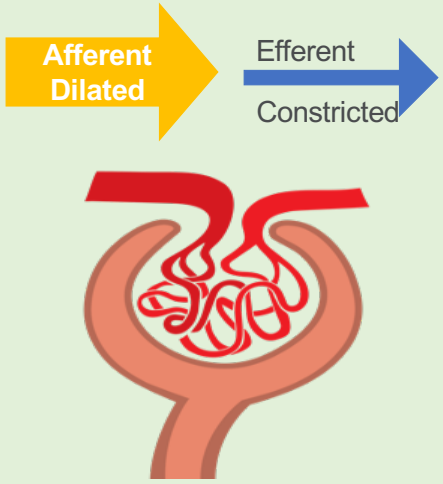


Includes all treated participants through 30 days after last dose.

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

Concurrent SGLT2 inhibition and ACEi could have potential for additive drop in GFR

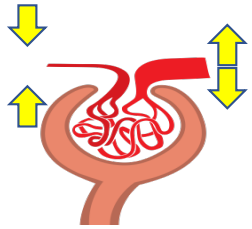
Diabetic Kidney



- More in, less out = increased pressure
- Hyperfiltration, proteinuria, and renal cell damage

Pharmacological actions:

SGLT2 inhibition + ACEi or ARB



Hemodynamic effects and clinical implications:

- Like being on both ACE/ARB and NSAIDS
  - Volume depletion can produce a substantial AKI in this setting
- Despite this concern, no increased risk of AKI seen in CREDENCE
  - May be in part because the treated group had much better overall renal status

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration

Adapted from: Skrtić M, et al. *Diabetologia* 2014;57:2599–602.

Patient Teaching Tool

Medication Changes When You Are Sick

BCRenal an agency of the Provincial Health Services Authority

If you have a bad flu or other illness which causes you to vomit or have diarrhea AND you cannot eat or drink normally, you may become dehydrated (dry). Dehydration can affect your kidney function and blood pressure.

If you are vomiting or have diarrhea or feel very sick:

- Try to drink fluids. It is best to drink fluids that do not have caffeine.

If you are so sick that you cannot drink your normal amount of fluids:

- Stop taking the medications listed below until you are able to start drinking fluids again.
- **Contact your doctor or nurse if you have to stop taking your medications for more than 2 days.**

- ☐ ACE inhibitor/Angiotensin receptor blocker: _____
- ☐ Anti-inflammatory: _____
- ☐ Metformin
- ☐ SGLT-2 inhibitor (e.g., Canagliflozin (Invokana®), Dapagliflozin (Forxiga®), Empagliflozin (Jardiance®)
- ☐ Water pill: _____
- ☐ Other: _____

Contact Phone Number: _____

Patients most likely to benefit from receiving this teaching sheet are those who:

- Experience episodes of vomiting or diarrhea
- Are planning to go travelling
- Have had acute kidney injury and/or were recently hospitalized

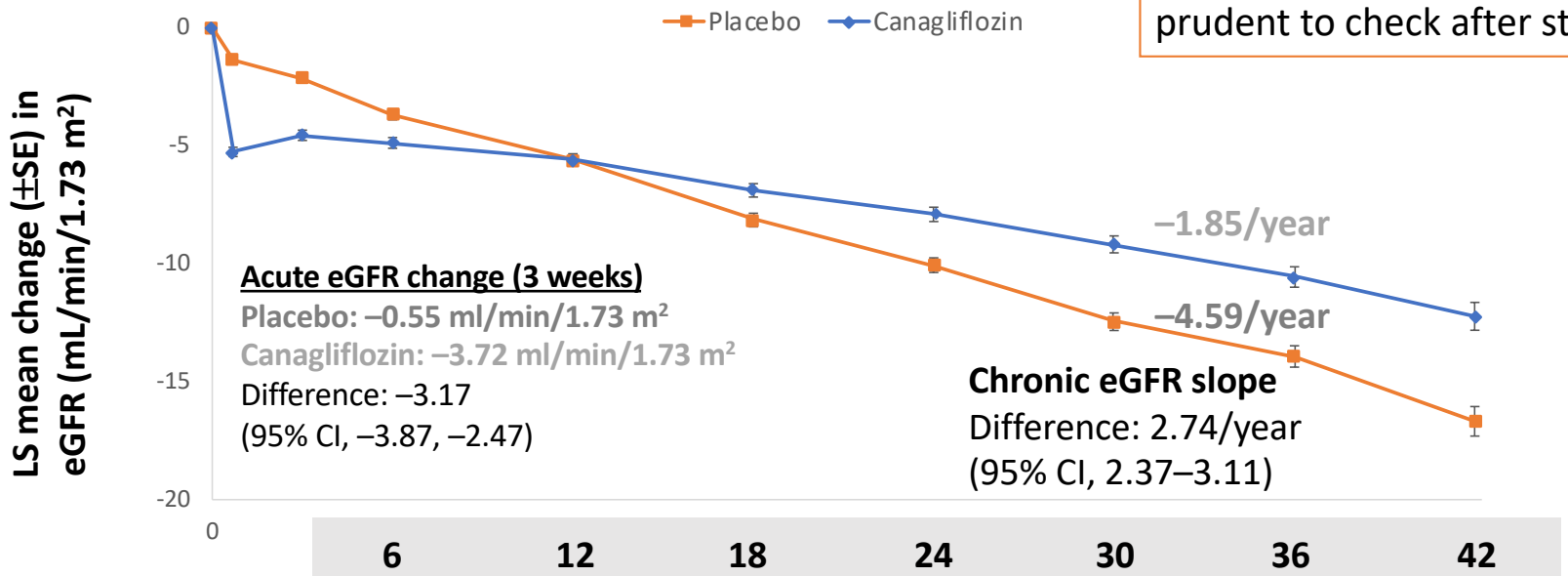
This brochure can be downloaded from the BC Renal Agency website: www.bcrenalagency.ca.

BC Renal Agency • Suite 700-1380 Burrard St. • Vancouver, BC • V6Z 2H3 • 604.875.7340 • BCRenalAgency.ca
Chronic Kidney Disease Symptom Management Resource
Aug 2017

A crucial safety mechanism in all of our patients, but especially when on combined treatments (like ACE/ARB and SGLT2i)

Effects on eGFR

Remember that an initial drop in GFR is expected
Similar to starting ACEi/ARB
Especially in lower GFR patients, prudent to check after starting



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.

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.

CREDENCE: Concomitant medications

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Glucose-lowering agents, %			
Insulin	66	65	66
Metformin	58	58	58
Sulfonylurea	28	30	29
DPP-4 inhibitor	17	17	17
GLP-1 receptor agonist	4	4	4
Renal and CV protective agents, %			
RAAS inhibitor	>99.9	99.8	99.9
Statin	70	68	69
Antithrombotic	61	58	60
Beta blocker	40	40	40
Diuretic	47	47	47

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

Does combination treatment alter treatment results or lead to AKI?

www.kidney-international.org clinical trial

Analysis from the EMPA-REG OUTCOME® trial indicates empagliflozin may assist in preventing the progression of chronic kidney disease in patients with type 2 diabetes irrespective of medications that alter intrarenal hemodynamics

see commentary on page 283

Gert J. Mayer[1], Christoph Wanner[2], Matthew R. Weir[3], Silvio E. Inzucchi[4], Audrey Koitka-Weber[2,5,6], Stefan Hantel[5], Maximilian von Eynatten[5], Bernard Zinman[7] and David Z.I. Cherney[8]

[1]Department of Internal Medicine IV (Nephrology and Hypertension), Medical University, Innsbruck, Austria; [2]Division of Nephrology, Würzburg University Clinic, Würzburg, Germany; [3]Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA; [4]Section of Endocrinology, Yale School of Medicine, New Haven, Connecticut, USA; [5]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [6]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia; [7]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada; and [8]Department of Medicine and Department of Physiology, Division of Nephrology, University Health Network, University of Toronto, Canada

SGLTi combined with RASB, diuretic, CCB, NSAID

Table 1 | Background medication use at baseline

Background medication, *n* (%)	Placebo (*N* = 2333)	Empagliflozin (*N* = 4687)
ACE inhibitor or angiotensin receptor blocker		
Yes	1868 (80.1)	3798 (81.0)
No	465 (19.9)	889 (19.0)
Any diuretic		
Yes	988 (42.3)	2047 (43.7)
No	1345 (57.7)	2640 (56.3)
Thiazide		
Yes	492 (21.1)	995 (21.2)
No	1841 (78.9)	3692 (78.8)
Loop diuretic		
Yes	364 (15.6)	725 (15.5)
No	1969 (84.4)	3962 (84.5)
Potassium-sparing agent	139 (6.0)	315 (6.7)
Calcium channel blocker		
Yes	788 (33.8)	1529 (32.6)
No	1545 (66.2)	3158 (67.4)
Nonsteroidal anti-inflammatory drug		
Yes	188 (8.1)	371 (7.9)
No	2145 (91.9)	4316 (92.1)

ACE, angiotensin converting enzyme.

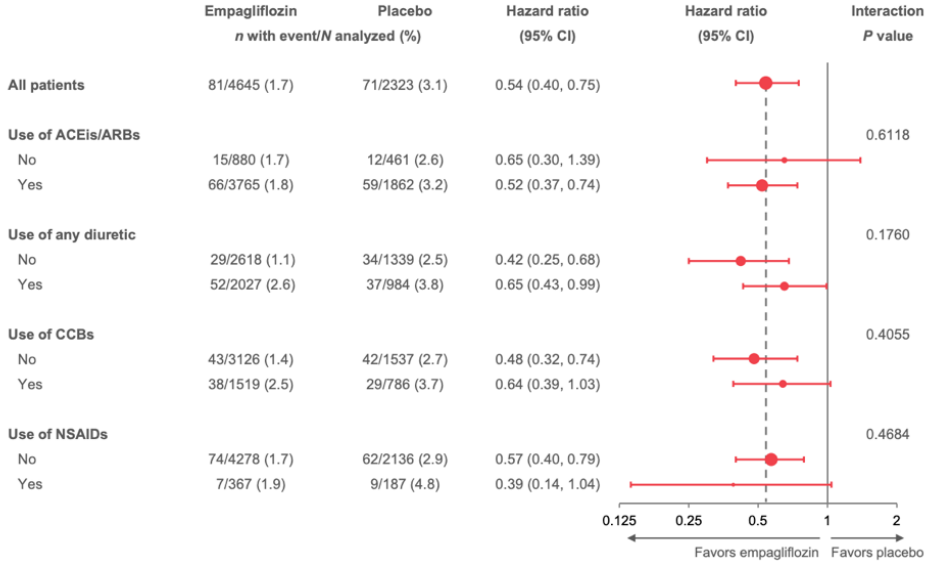


Figure 2 | Doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease by background medication use at baseline. Serum creatinine accompanied by estimated glomerular filtration rate ≤45 ml/min per 1.73 m^2; Cox regression analysis in patients treated with ≥1 dose of study drug. Estimated glomerular filtration rate assessed by Modification of Diet in Renal Disease formula. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.

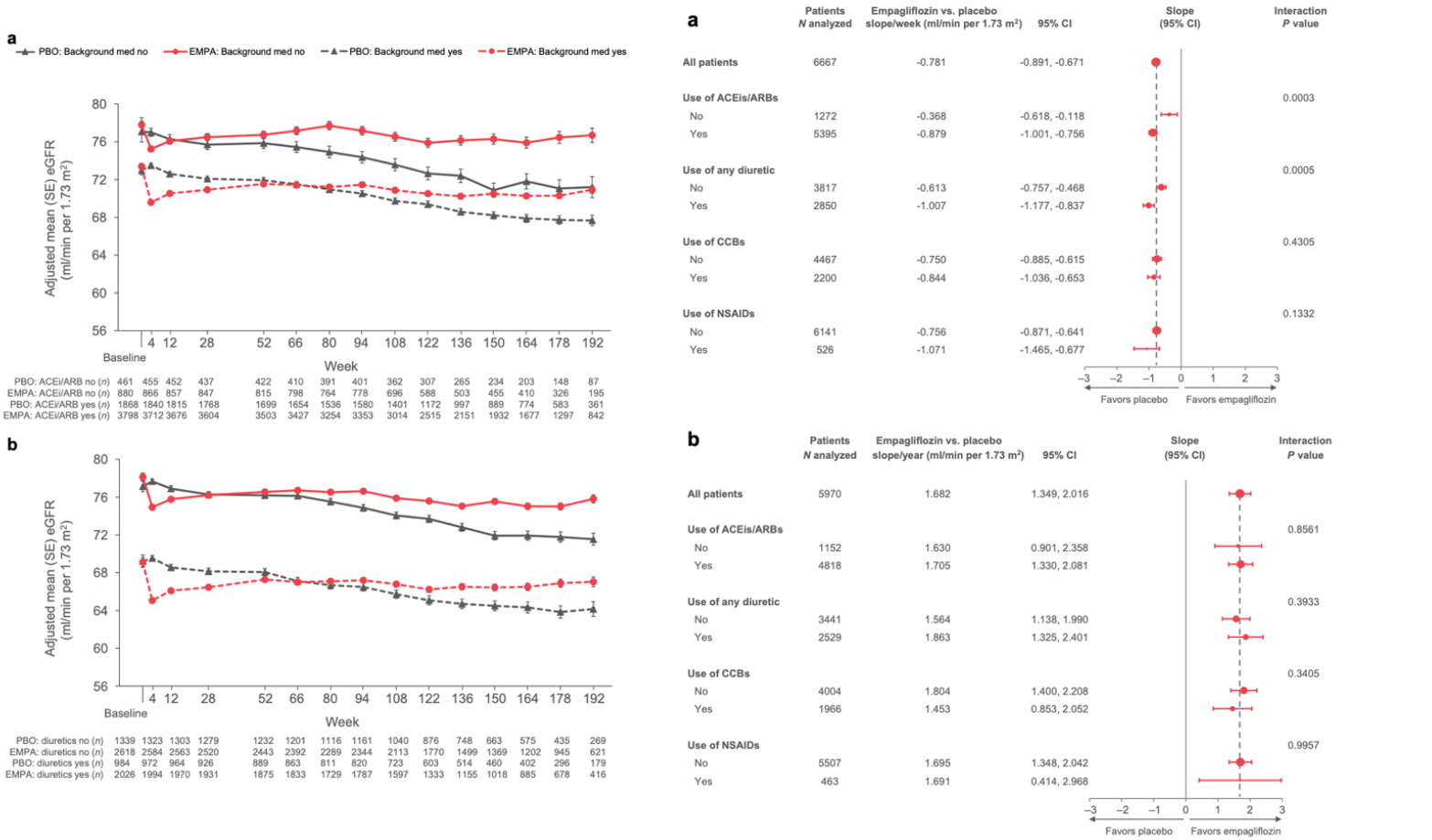


Figure 5 | Change in estimated glomerular filtration rate values over prespecified periods by background medication use at baseline: (a) baseline to week 4; (b) week 4 to last value on treatment; and (continued)

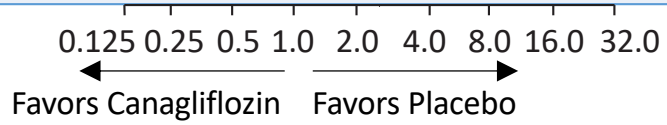
Higher initial drop in GFR (significant with RASB, diuretic, non-sig with CCB and NSAID)

Despite this

- No difference in treatment benefit at end of trial
- No difference in rate of AKI
- No difference in rate of drug discontinuation

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)



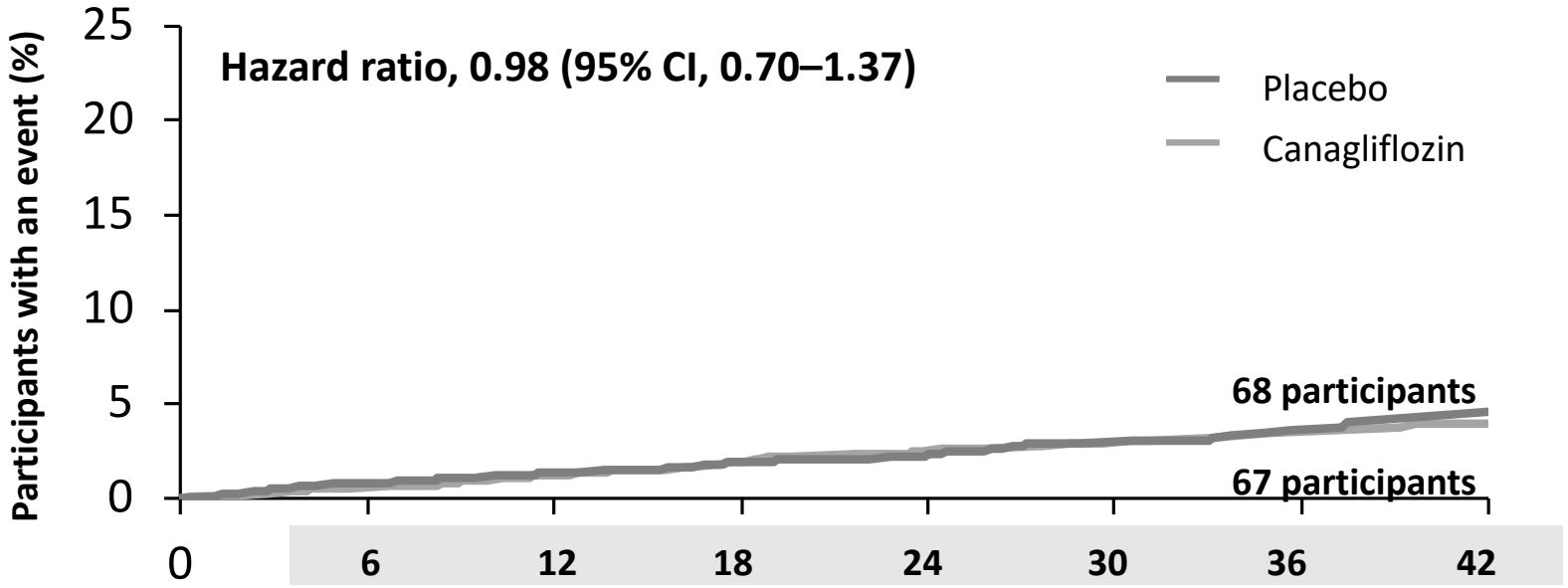
Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*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: Fracture

Concern in prior SGLT2i trials, not seen in CREDENCE



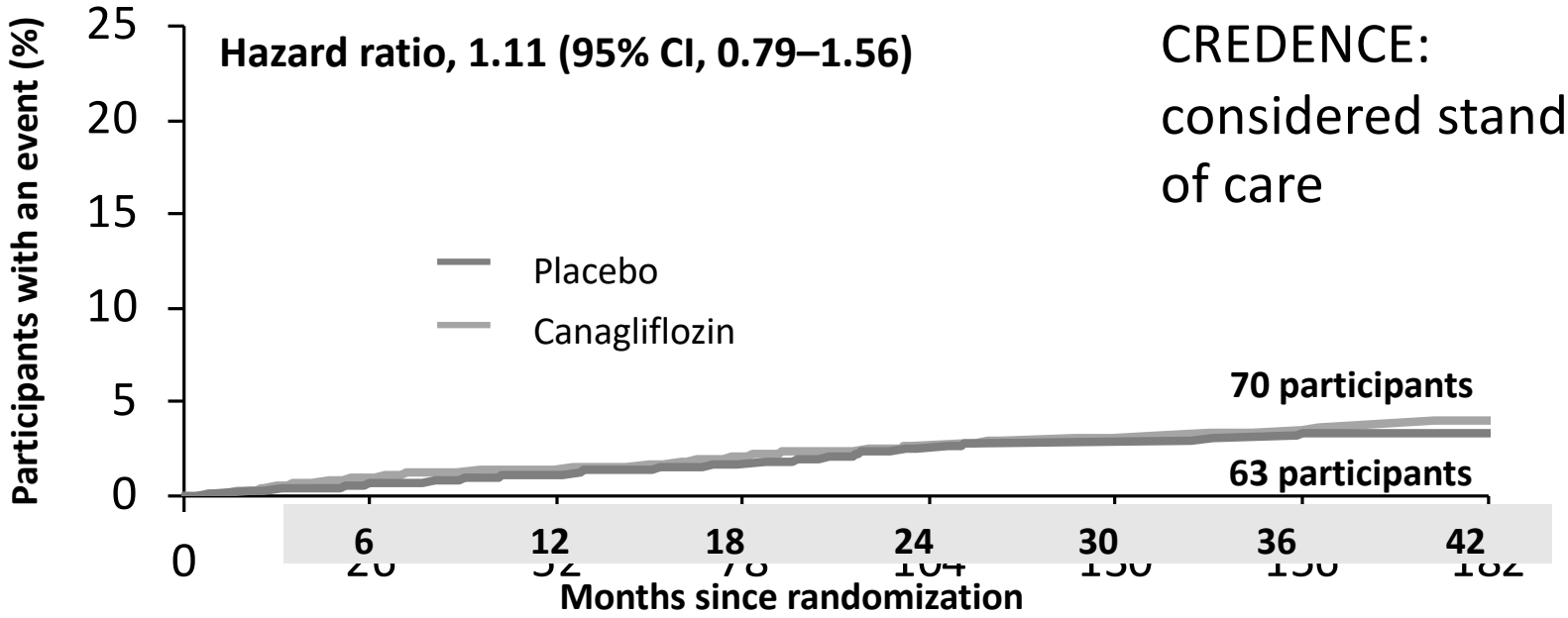
No. at risk								
Placebo	2197	2166	2128	2061	1769	1178	656	176
Canagliflozin	2200	2171	2121	2074	1785	1225	668	200

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

AEs: Lower extremity amputation

Concern in prior SGLT2i trials, not seen in CREDENCE

Routine foot checks were included in CREDENCE: considered standard of care



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.

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.

Summary: Safety

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

Putting all together

- SGLT2i represent an additional mechanism for delaying decline in DKD
- The dedicated CREDENCE trial demonstrated impressive, clinically important benefits in renal outcomes
  - Effect on top of RASB
  - These medications are safe, including in combination treatment
  - Remember the 'Sick Day' medication list

- Not yet firmly recommended as standard of care, but that is likely coming – in the CREDENCE like population (GFR >30, ACR>30)
- Coverage can sometimes be an issue

Stay tuned: Update on Renal Outcomes Trials

CREDENCE[1,2]	DAPA-CKD[3]	EMPA-KIDNEY[4]
Stopped early based on the achievement of pre-specified efficacy criteria	Ongoing, estimated completion Nov 2020	Ongoing, **estimated completion June 2022**

Will include:

- Lower ranges of GFR
- Lower ranges of protein
- *Non-diabetic* CKD

1. ClinicalTrials.gov Identifier: NCT02065791; 2. Jardine MJ et al., *Am J Nephrol* 2017;46:462–472.
3. ClinicalTrials.gov Identifier: NCT03036150; 4 ClinicalTrials.gov Identifier: NCT03594110.

Questions/Discussion