2021 ACOI Annual Convention
And Scientific Sessions
October 27-30

Filtering Out The Potential Role Of SGLT2 Inhibitors For The Management Of Chronic Kidney Disease

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Disclosures

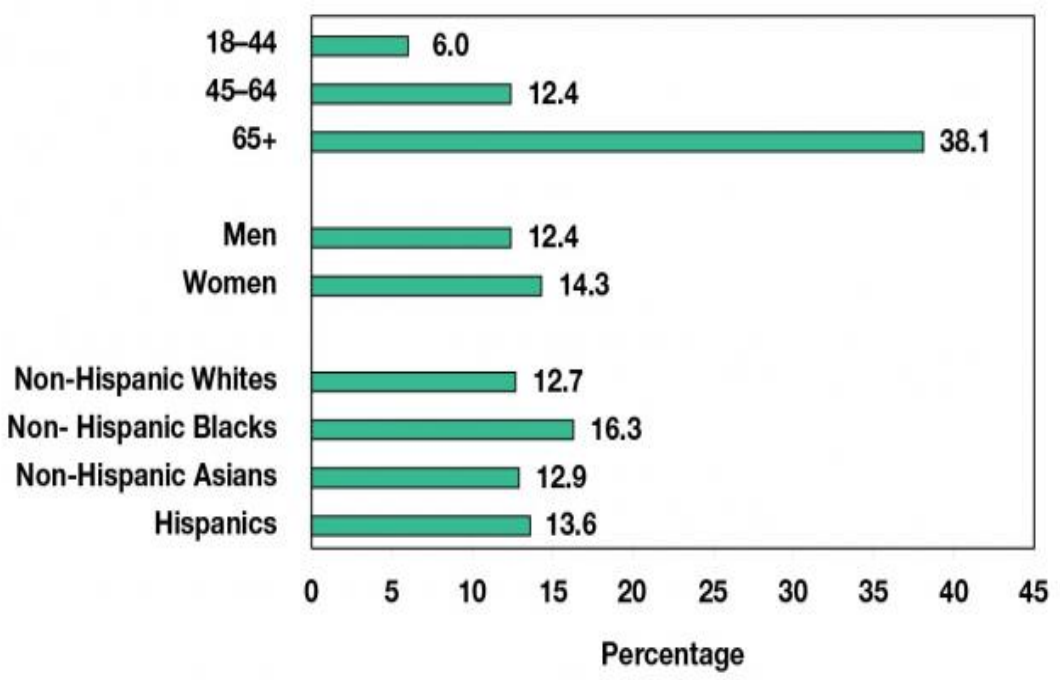
- None

Objectives

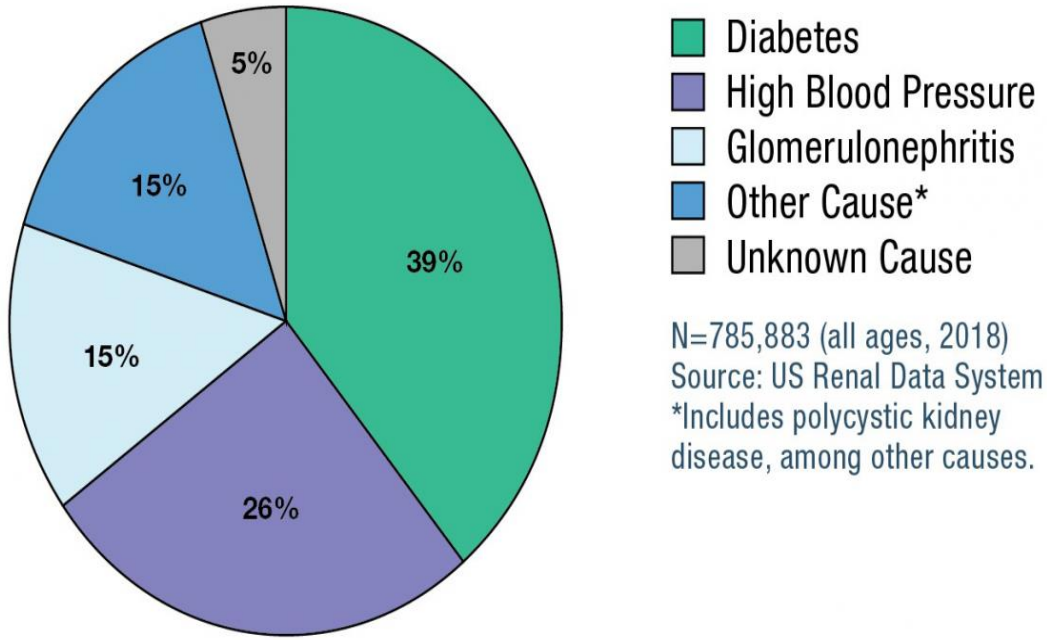
- Explain the burden of chronic kidney disease
- Review the pathophysiology of diabetic nephropathy
- Understand the mechanism of SGLT2 inhibitors in the management of CKD
- Evaluate the clinical trial data for SGLT2 inhibitors and renal outcomes
- Summarize the role of SGLT2 inhibitors in clinical practice

The Burden of Chronic Kidney Disease (CKD)

Percentage of US ADULTS aged 18 years or older with CKD



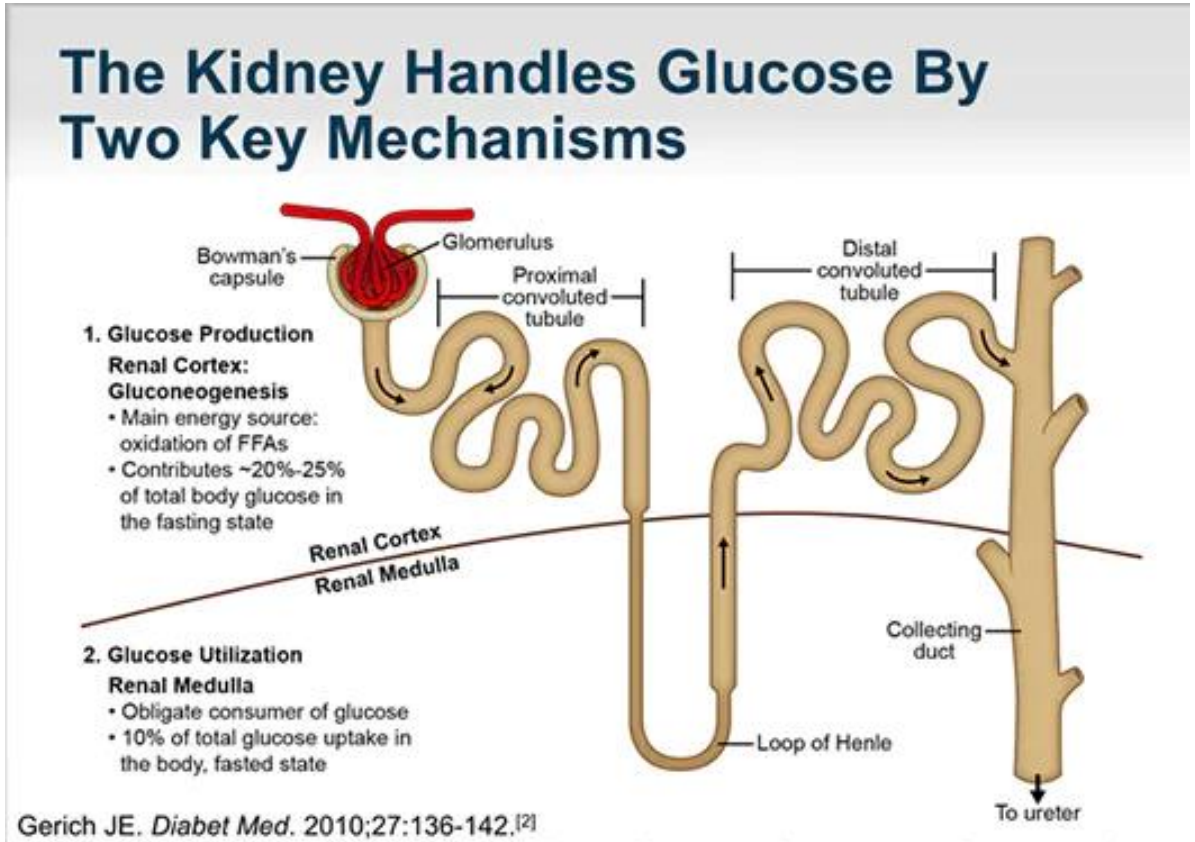
Reported Causes of End-Stage Renal Disease (ESRD) in the United States



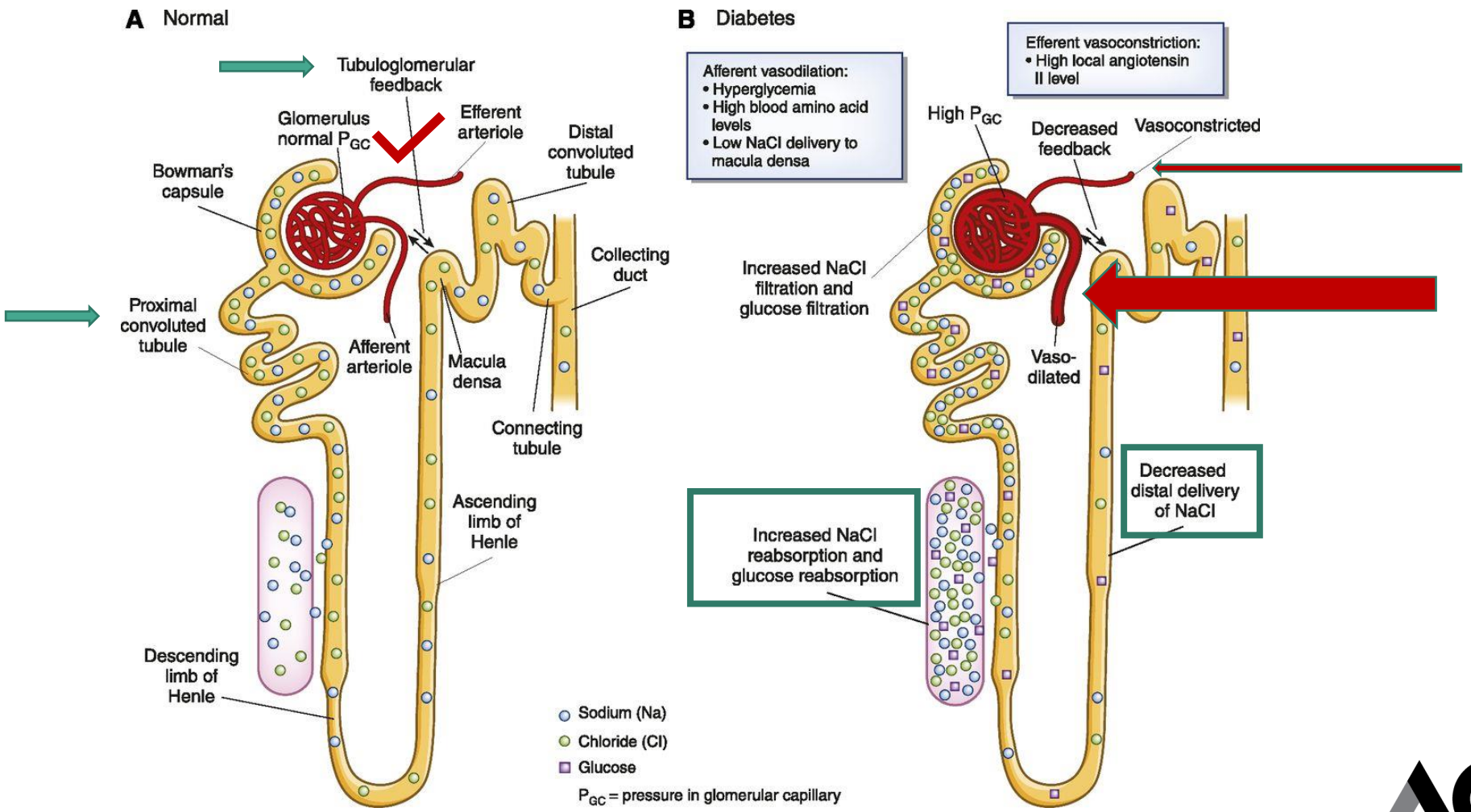
Center for Disease Control and Prevention. *Chronic Kidney Disease in the United States,* 2021

Kidney Physiology

- 20-25% of the total body's glucose is released by the kidneys
- Approximately 180 grams of glucose is filtered by the kidneys everyday
- Mostly all of it is reabsorbed by sodium-glucose co-transporter 2 expressed in the proximal tubules



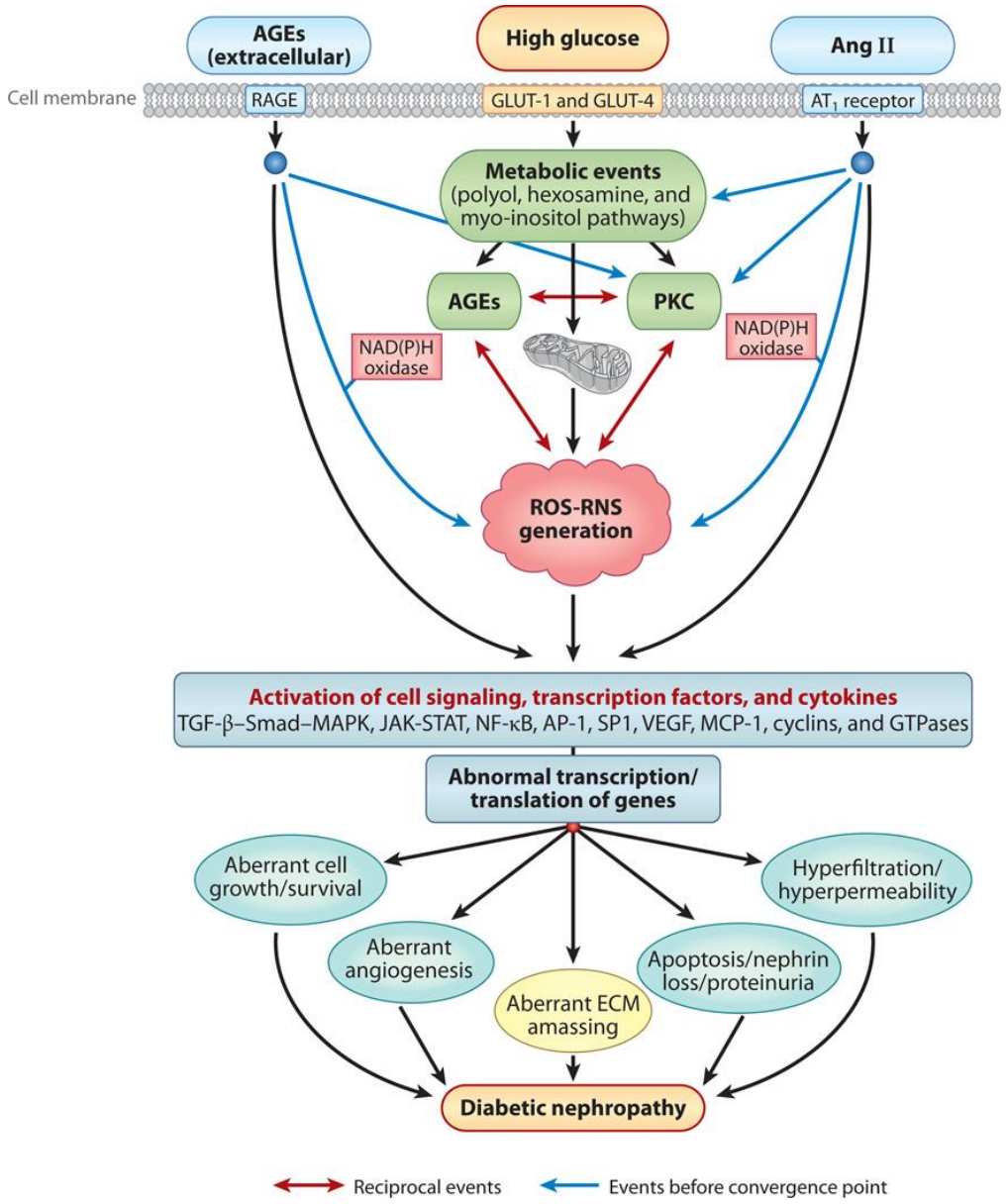
Normal & Diabetic Nephron



Radica Z. Alicic et al. CJASN 2017;12:2032-2045

Diabetic Nephropathy

- Hyperfiltration
- Silent
- Microalbuminuria
- Macroalbuminuria
- Renal Impairment



KDIGO 2012

GFR categories (mL/min per 1.73m²)			Albuminuria (ACR) categories (mg/g)		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30	30–300	>300
G1	Normal or high	≥90			
G2	Mildly decreased	60–89			
G3a	Mildly to moderately decreased	45–59			
G3b	Moderately to severely decreased	30–44			
G4	Severely decreased	15–29			
G5	Kidney failure	<15			

Kidney International 2021 99S1-S87DOI: (10.1016/j.kint.2020.11.003)

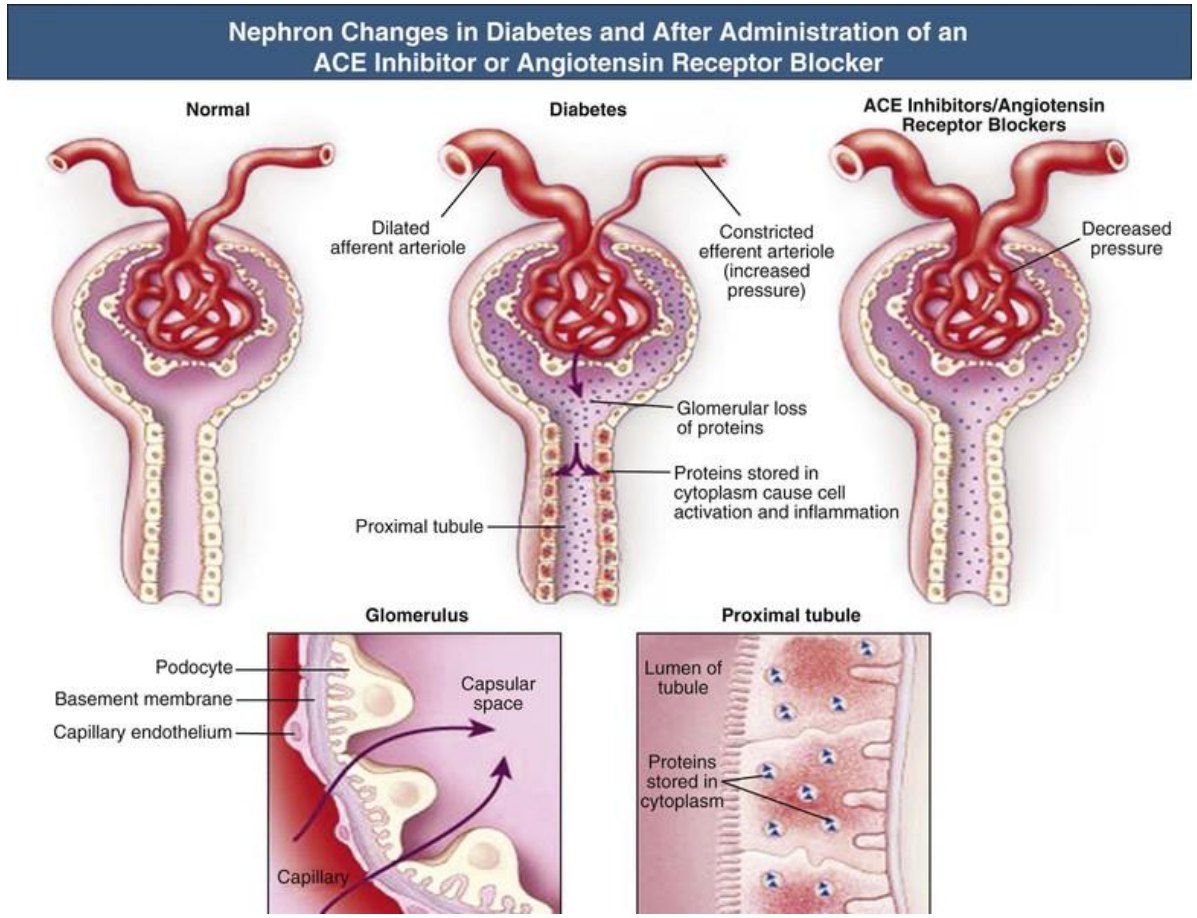
Renin-Angiotensin-System Inhibitors

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)

- ✓ Reduce blood pressure
- ✓ Reduce proteinuria

IDNT Study

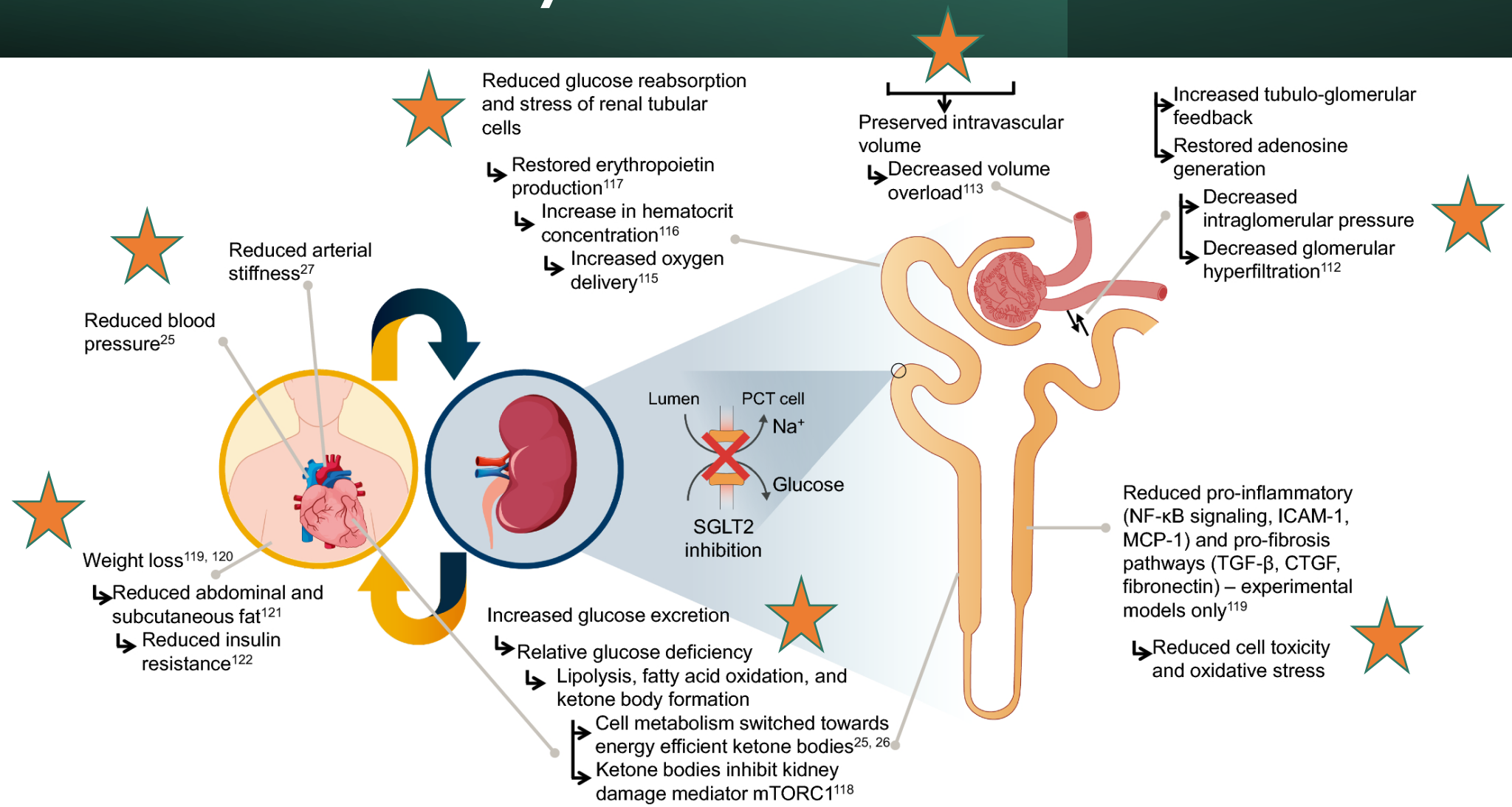
RENAAL Study



Wolf, Sharma. Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Nephropathy.

1. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001; **345**: 851-860
2. Brenner BM, Cooper ME, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001; **345**: 861-869

The Role of SGLT2 Inhibitors in Chronic Kidney Disease



Giorgino F, Vora J, Fenici P, Solini A. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol*. 2020

Summary of Normal and Diabetic Kidneys

- Hyperfiltration initiates diabetic kidney disease mediated by SGLT2
- Proteinuria reduction provides renal protection
- Angiotensin blockade improves outcomes
- Blood pressure control improves renal outcomes
- Glycemic control improves microvascular disease outcomes

FDA Approved Indications for SGLT2-I

(May 2021)

Indication	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Antiglycemic	**As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**			
CV disease	Reduce the risk of Major Adverse Cardiovascular Events in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) MACE: cardiovascular death, nonfatal myocardial infarction and nonfatal stroke)	Reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple risk factors	Reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.	
Heart Failure	(partial – see below)	**Reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction NYHA II-IV**	**Approved in patients with HF with reduced ejection fraction**	
Renal Disease	Reduce the risk of end-stage kidney disease doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day	**Breakthrough Therapy Designation (BTD) in the US for patients with CKD with and without type-2 diabetes**	**Approved in patients with CKD and HFrEF**	

FDA Approved Indications for SGLT2-I

	Canagliflozin (®Invokana)	Dapagliflozin (®Farxiga)	Empagliflozin (®Jardiance)	Ertugliflozin (®Steglatro)
Doses	100 mg, 300 mg	5 mg, 10 mg	10 mg, 25 mg	5 mg, 15 mg
eGFR>60	No change	No change	No change	No change
eGFR 45-60	**100 mg only**	**No change**	**No change**	**Don't start**
eGFR 30-45	**Don't start (cont 100 mg)**	**Don't start**	**Don't start**	**Don't start**
eGFR <30	**Only 100 mg QD if Albuminuria>300mg/g**	***GFR>25: Can initiate in HF or CKD, continue <25**	**Only in patients with HFrEF**	**Contraindicated**
FDA Approved	March 2013	January 2014	August 2014	December 2017

Cardiovascular Safety Trials

Trials	#N & Follow-Up	Mean A1c%	Mean eGFR (ml/min/1.73 m^2)	Primary Outcome
DECLARE-TIMI 58	17,160 4.2 years	8.3%	85.2	3-P MACE Composite of CV death or HHF
CANVAS	10,142 3.6 years	8.3%	76.5	3-P MACE
EMPA-REG	7020 3.1 years	8.1%	74	3-P MACE
VERTIS-CV	8238 3.5 years	8.2%	76	3-P MACE

Williams DM, Nawaz A, Evans M. Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors: *Diabetes Ther*. 2021

Cardiovascular Safety Trials: Meta Analysis

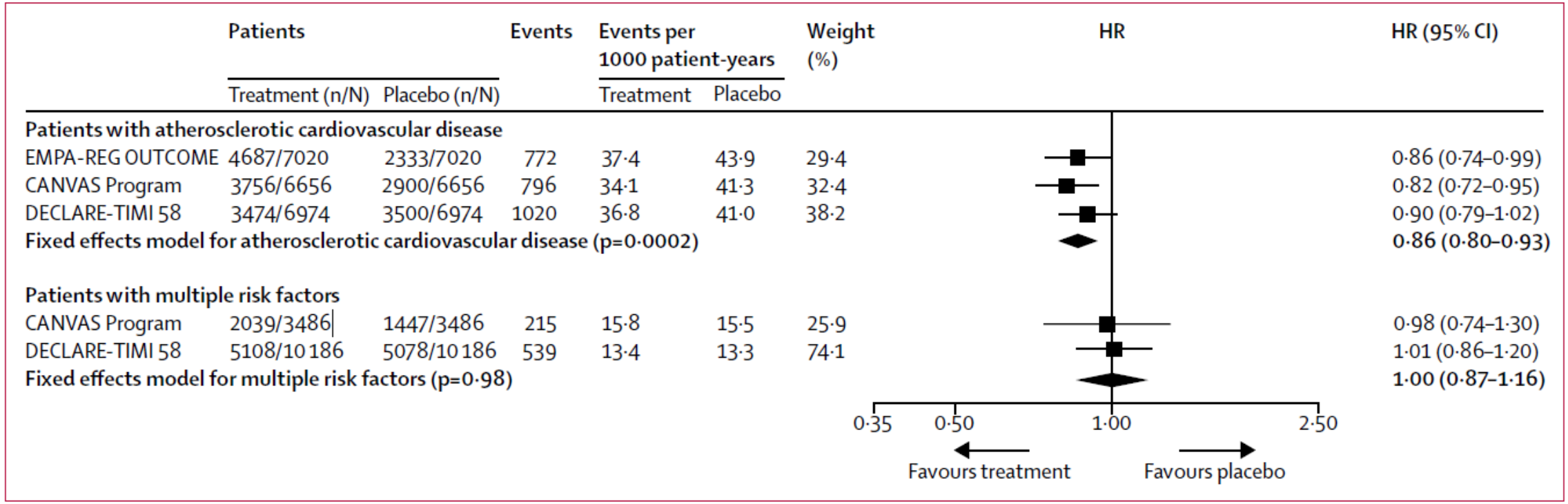


Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

Zelniker, Thomas A et al. The Lancet, Volume 393, Issue 10166, 31 - 39

Cardiovascular Safety Trials: Meta Analysis

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**

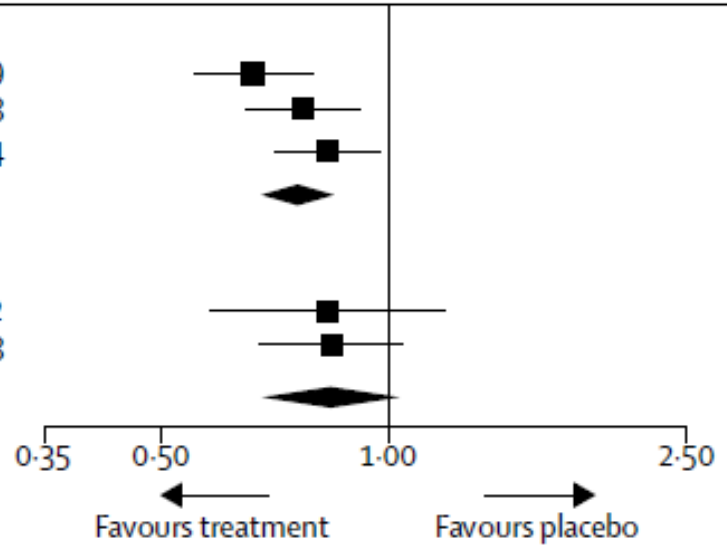
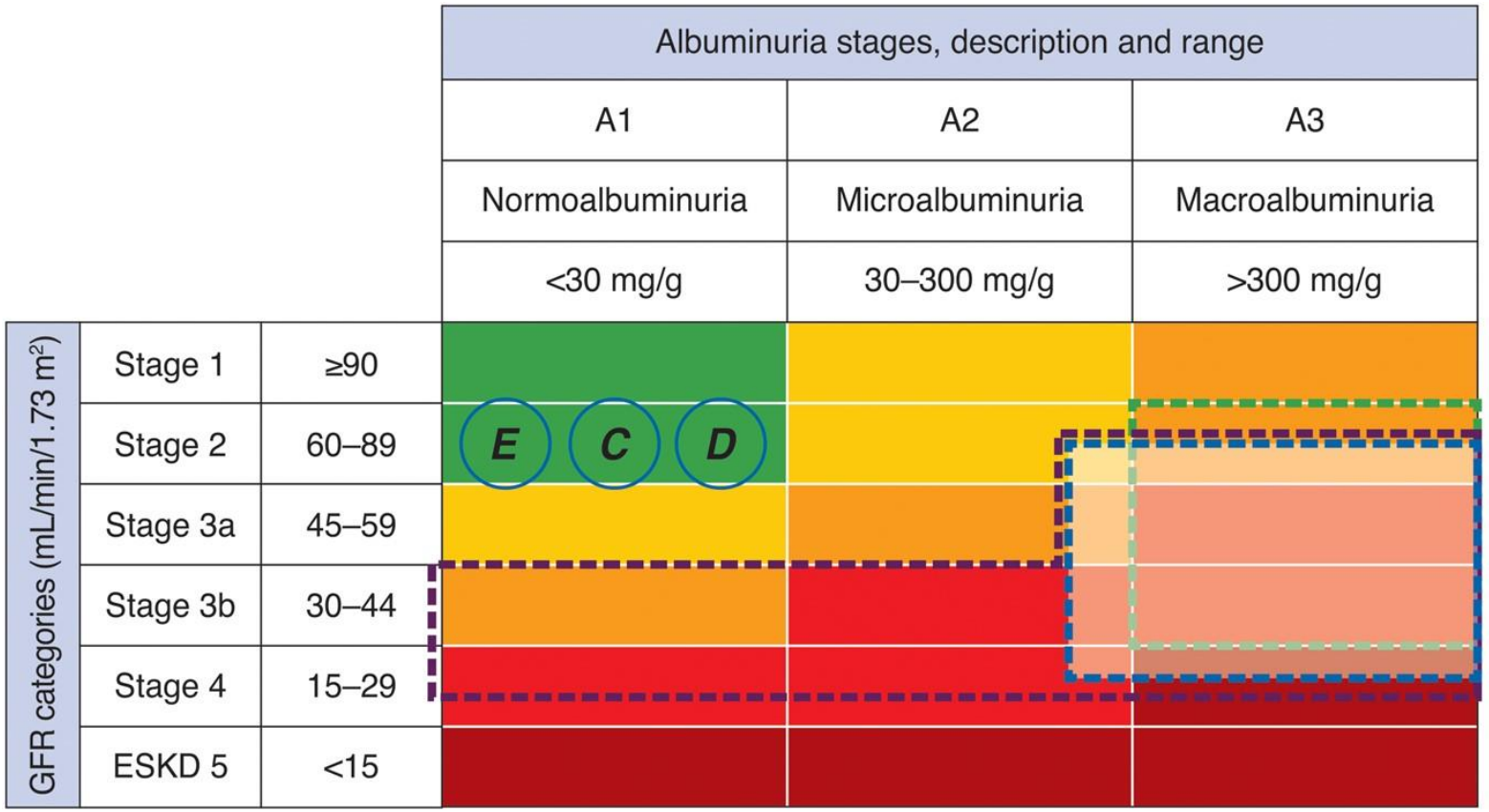


Figure 2: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease

EMPA-REG[1]	CANVAS Program [2]	DECLARE-TIMI 58 Trial [3]
• New-onset macroalbuminuria • Doubling of serum creatinine • (+eGFR <45 ml/min/1.73 m2) • Initiation of RRT • Death due to renal disease	• Albuminuria progression • Albuminuria regression • 40% reduction in eGFR • End-stage renal disease • Renal death	• Decreased of 40% or more eGFR • EGFR drop to <60 ml/min/1.73m2 • New end-stage renal disease • Death from renal or CV causes
38% reduction in "incident or worsening nephropathy"	40% reduction in composite of >40% reduction in eGFR, requirement for RRT and death from renal cause	24% reduction in composite of >40% reduction in eGFR, new ESRD or death from renal or CV causes

Wanner, C., S. E. Inzucchi, et al. (2016). New England Journal of Medicine **375(4): 323-334.**
Perkovic, V., D. de Zeeuw, et al. (2018). The Lancet Diabetes & Endocrinology **6(9): 691-704**
Mosenzon, O., S. D. Wiviott, et all, The Lancet Diabetes & Endocrinology. 2019

SGLT2 Inhibitor Trial – Renal Focus



CREDENCE (DKD only)
eGFR ≥30 to <90 mL/min/1.73 m²
and UACR ≥300 mg/g

DAPA-CKD (CKD)
eGFR ≥25 to <75 mL/min/1.73 m²
and UACR ≥200 mg/g

EMPA-KIDNEY (CKD)
eGFR ≥45 to <75 mL/min/1.73 m²
and UACR ≥200 mg/g
OR
eGFR ≥20 to <45 mL/min/1.73 m²

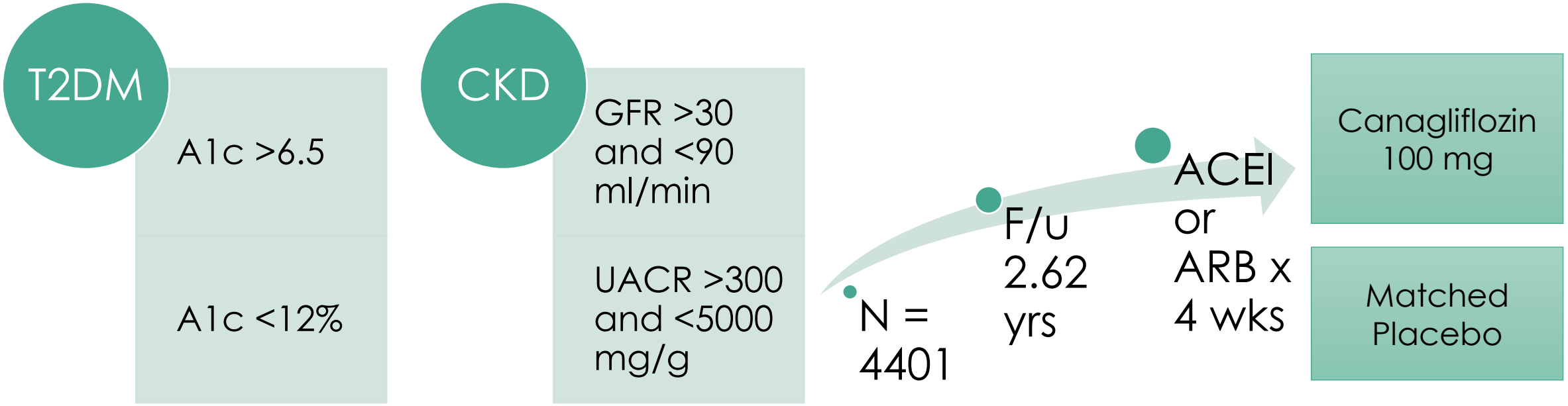
E=EMPA-REG OUTCOME; C=CANVAS; D=DECLARE-TIMI 58

Renal & Cardiac Outcome Trials

Trials	#N & Follow-Up	Mean A1c%	Mean eGFR (ml/min/1.73 m2)	Primary Outcome
DAPA-CKD	**4304 2.4 years**	**T2DM: 67% Non DM: 33%**	**43.1**	**Composite of sustained ≥ 50% eGFR decline, ESRD, renal death or CV death**
CREDENCE	**4401 2.6 years**	**8.3%**	**56.2**	**A composite of ESRD, doubling serum creatinine, or death from renal or CV disease**
DAPA-HF	4744 1.5 years	T2DM: 42% Non DM: 58%	65.8	Composite of worsening HF or CV Death
EMPEROR Reduced	3730 1.2 years	T2DM: 50% Non DM: 50%	62	A composite of CV death or HHF

Williams DM, Nawaz A, Evans M. Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors: *Diabetes Ther*. 2021

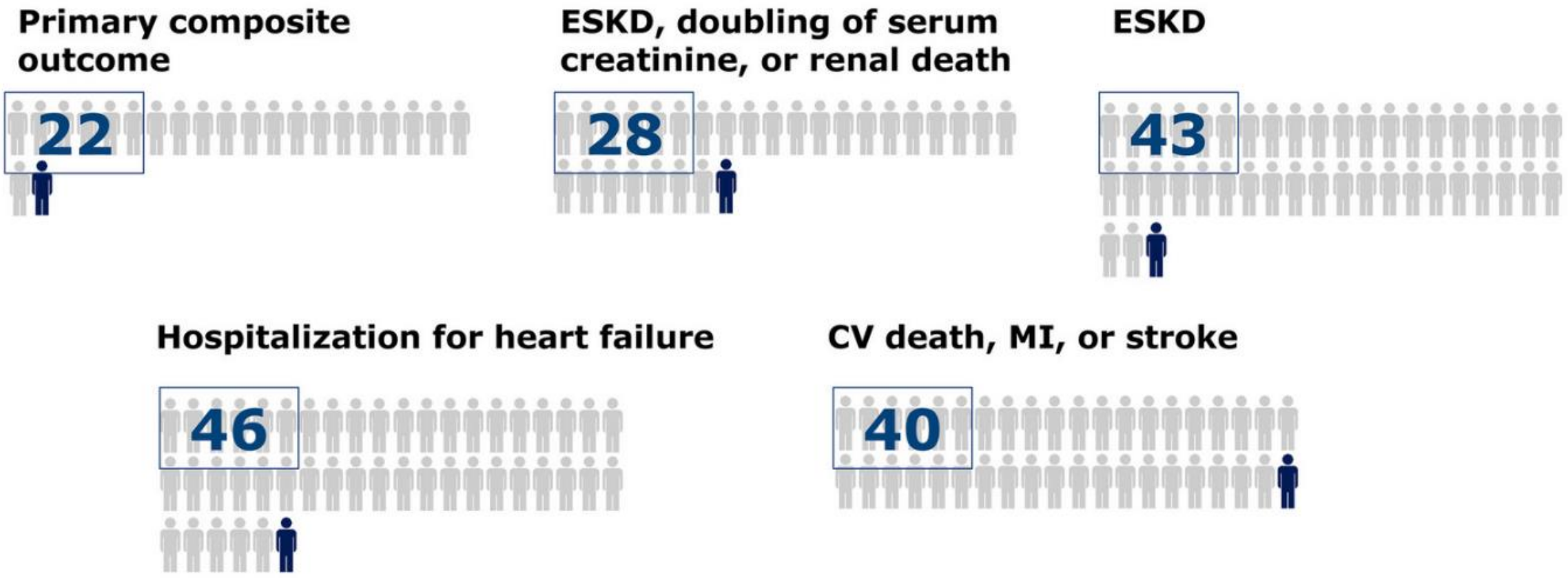
CREDENCE



The primary outcome was a composite of

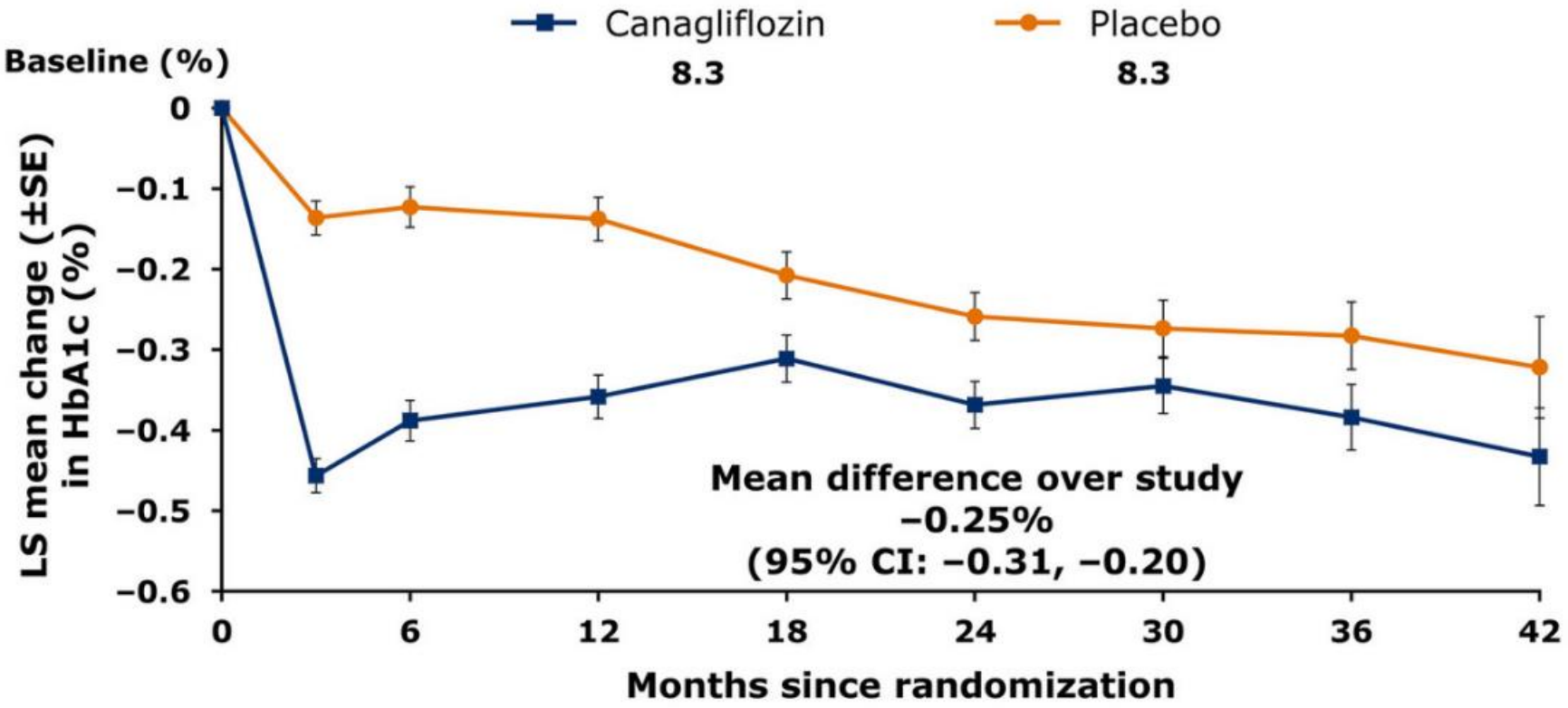
- end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30 days),
- doubling of the serum creatinine level from baseline sustained for at least 30 days, or
- death from renal or cardiovascular disease.

CREDENCE



Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE (CANVAS)



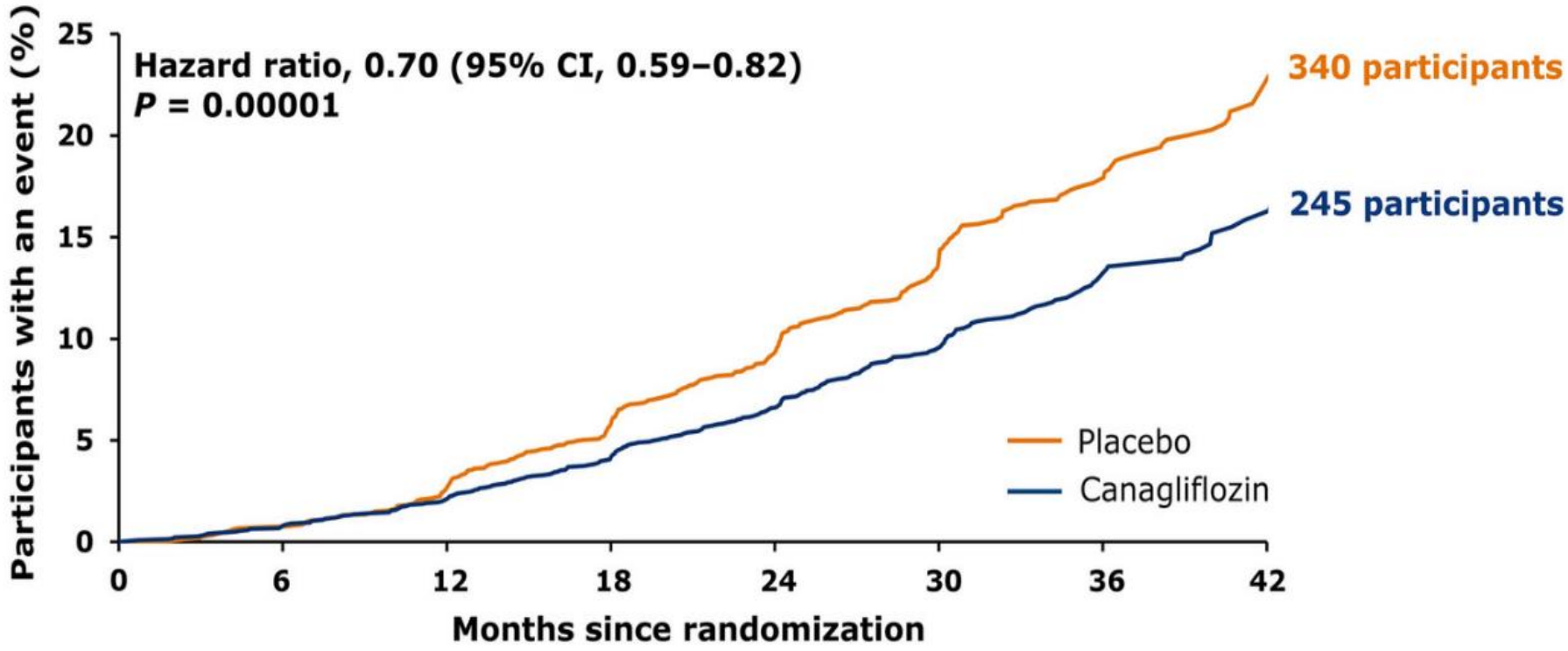
No. of participants

Placebo	2150	2103	2066	1981	1882	1728	1172	688	252
Canagliflozin	2154	2108	2074	2024	1909	1817	1254	729	274

Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE

Primary Outcome: ESRD, Doubling of Serum Creatinine, or Renal or CV Death

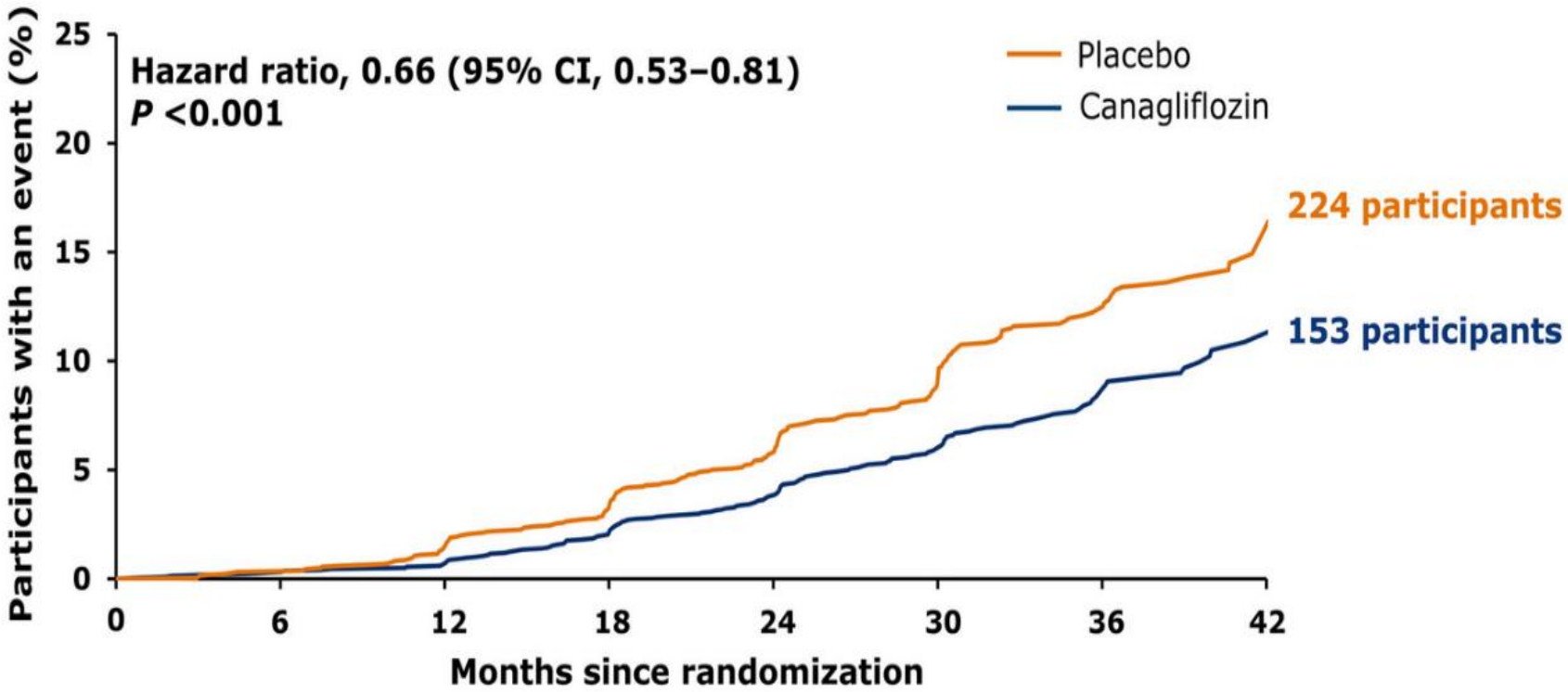


No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE

ESKD, Doubling of Serum Creatinine, or Renal Death

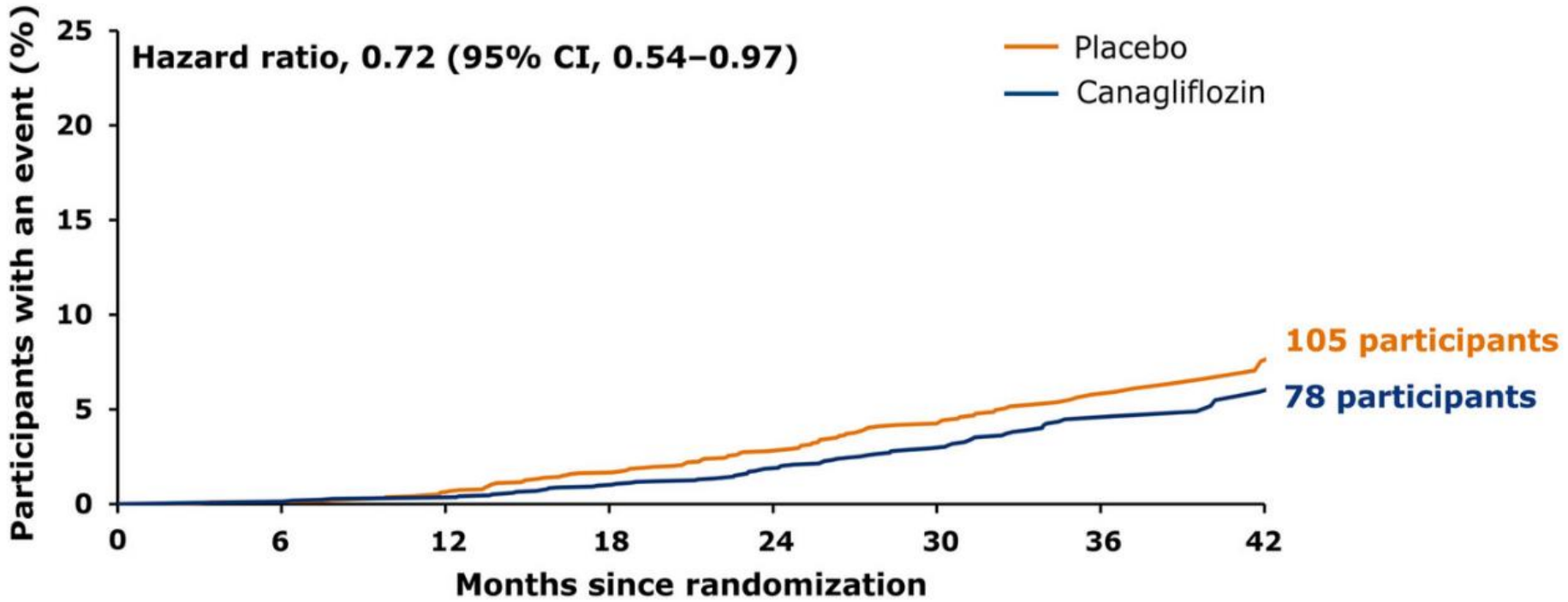


No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE

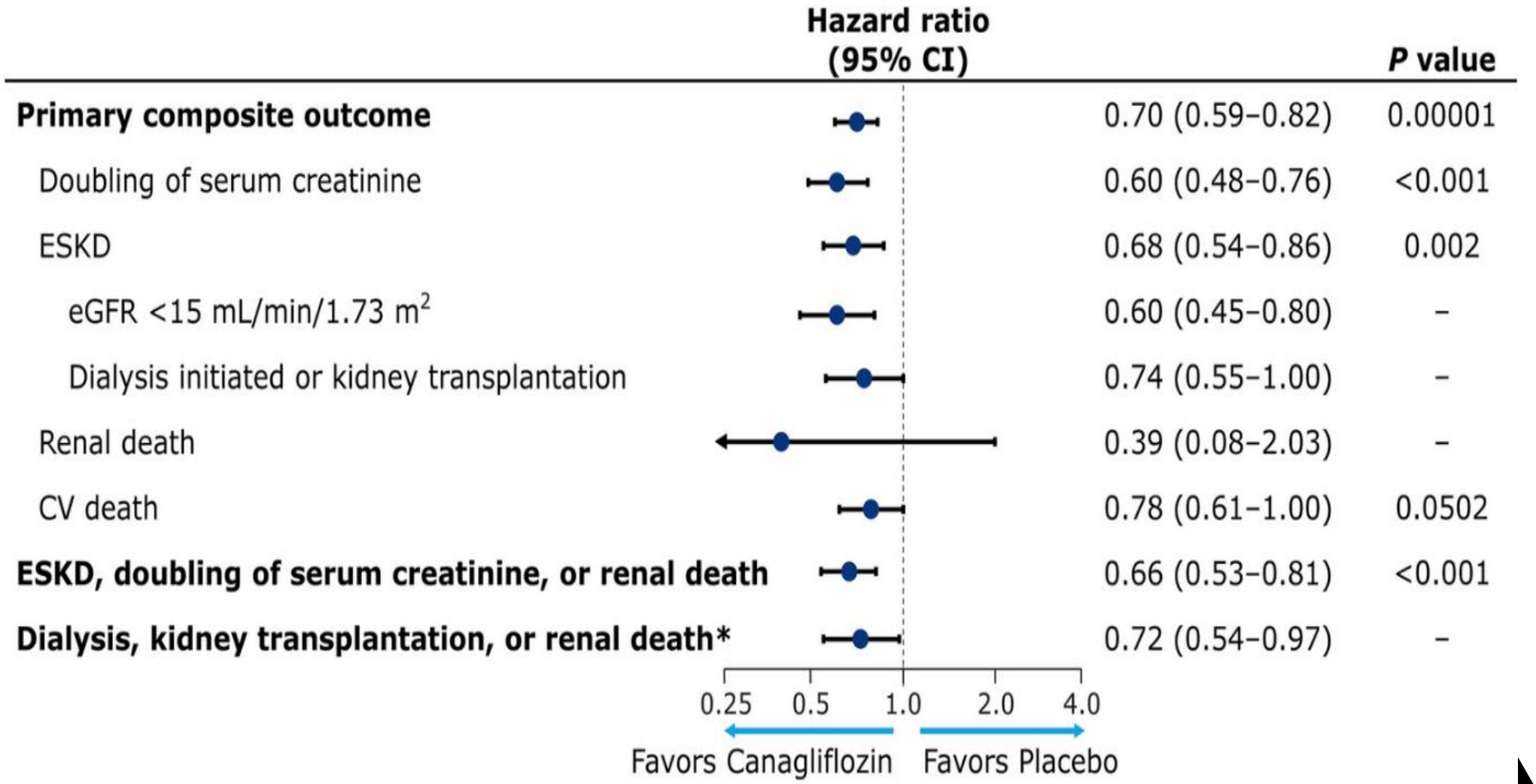
Dialysis, Kidney Transplantation, or Renal Death



No. at risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

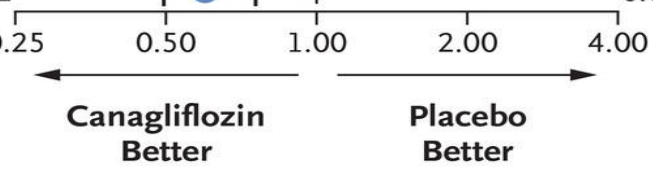
CREDENCE



Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE

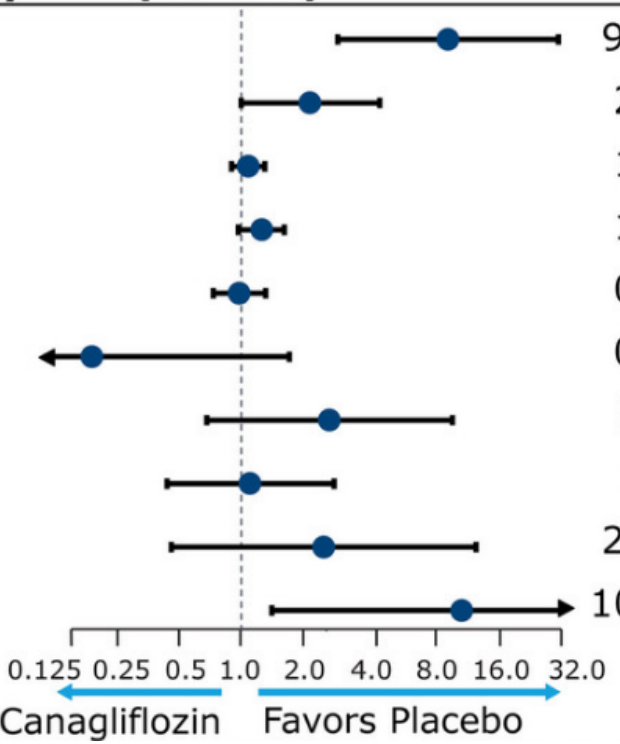
Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m²	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m²	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m²	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	



Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE – All AE

	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)

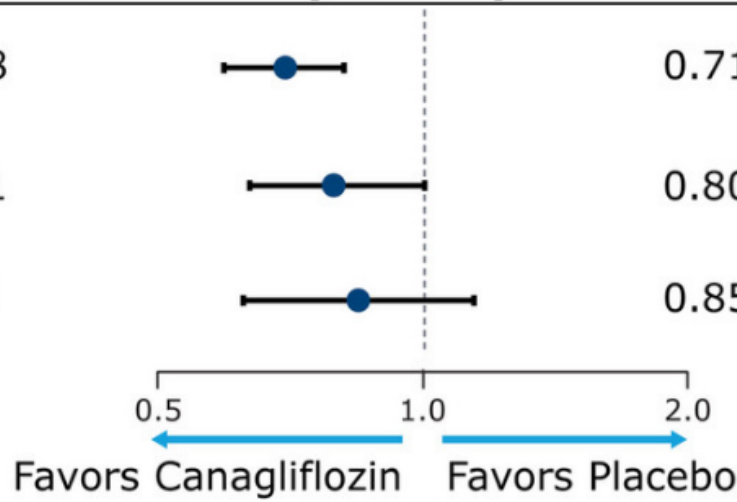


Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

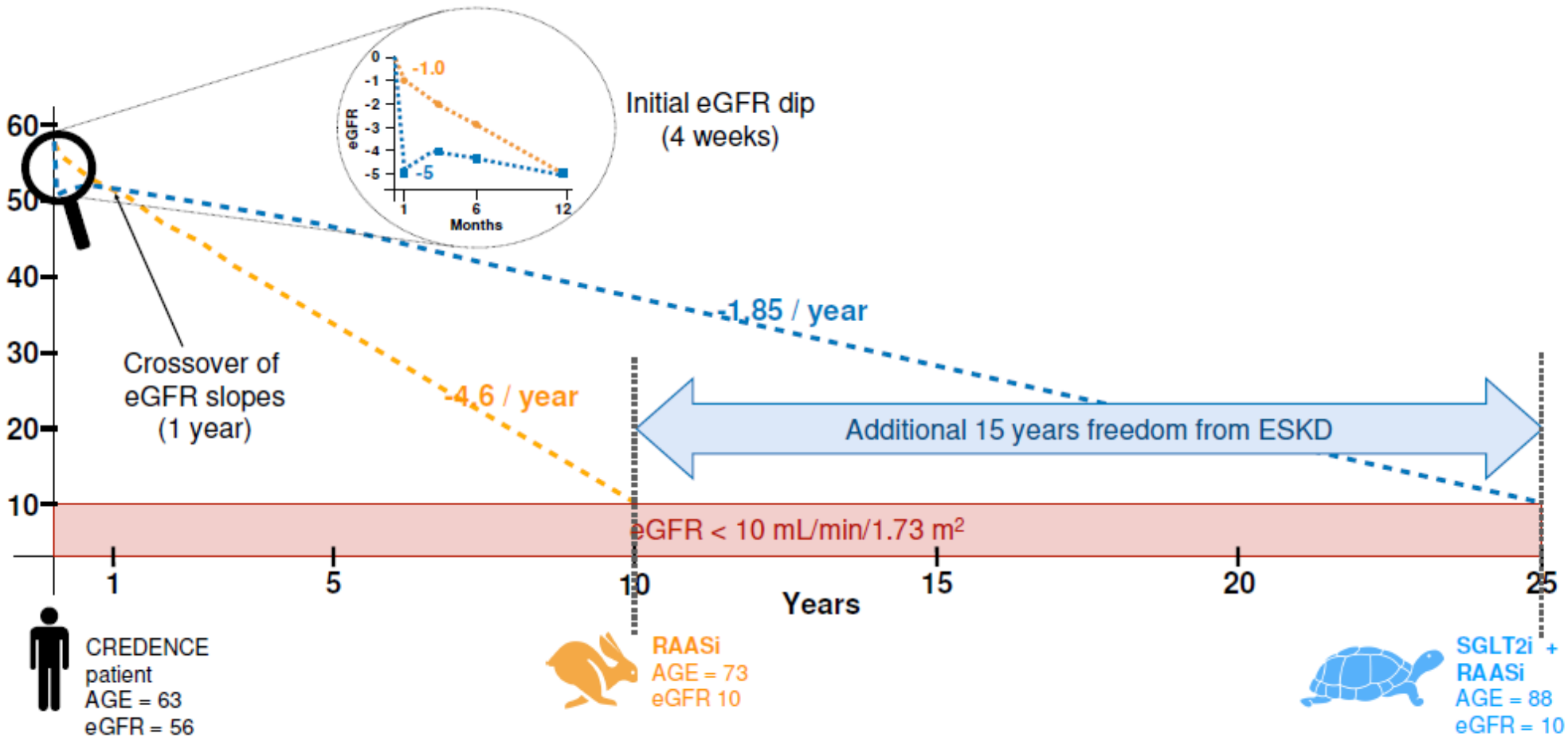
CREDENCE – Renal AE

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



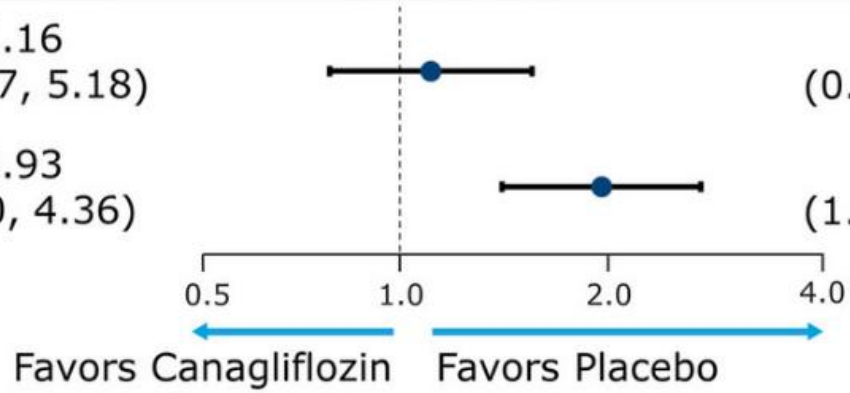
Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

Induced Acute Kidney Injury



CREDENCE – Lower Extremity Amputation

	Participants with an event per 1000 patient-years (n/N)		IRD per 1000 patient-years (95% CI)	Hazard ratio (95% CI)
	Canagliflozin	Placebo		
CREDENCE	12.3 (70/2200)	11.2 (63/2197)	1.16 (−2.87, 5.18)	1.11 (0.79–1.56)
CANVAS Program[1]	6.3 (140/5790)	3.4 (47/4344)	2.93 (1.50, 4.36)	1.97 (1.41–2.75)



Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE - SUMMARY

- Canagliflozin reduced the risk of primary outcomes of ESRD, doubling of serum creatinine, or renal or CV death by 30% (P=0.00001)
- Canagliflozin also reduced the risk of secondary outcomes of ESRD, doubling of serum creatinine, or renal death by 34% (P<0.001)

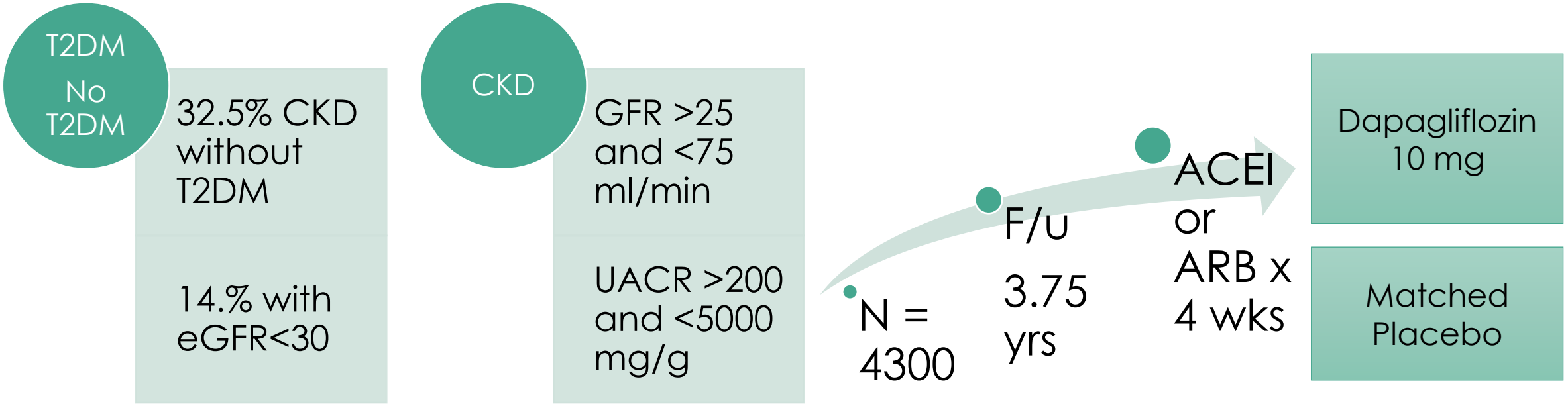
Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

CREDENCE - SUMMARY

- Similar risk reductions were seen for exploratory outcomes assessing components of the primary outcome:
  - ESRD: 32% lower
  - Dialysis, transplantation, or renal death: 28% lower
- Canagliflozin attenuated the slope of chronic eGFR decline by 2.7ml/min/1.73m2/year

Perkovic, V., M. J. Jardine, et al. (2019). *NEJM*

DAPA-CKD



The primary outcome was the first occurrence of any of the following:

- A decline of at least 50% in the eGFR
- The onset of end stage kidney disease (dialysis maintained for >28 days, kidney transplantation, or an eGFR < 15 ml/min confirmed by serial measurement after 28 days)
- Death from renal or CV cause

DAPA – CKD: Secondary Outcomes

- Time to a composite renal endpoint:
  - ≥50% eGFR decline from baseline
  - ESRD defined as eGFR <15 mL/min/1.73 m2, need for chronic dialysis or renal transplantation
  - Renal death
- Time to the first occurrence of either cardiovascular death or hospitalization for heart failure
- Time to death from any cause

Heerspink et al. Dapagliflozin in patients with chronic kidney disease. NEJM, 2020

DAPA – CKD: Baseline Characteristics

Characteristic	Overall (*N* = 4304)	With T2D (*n* = 2906)	Without T2D (*n* = 1398)
Age (years), mean (SD)	61.8 (12.1)	64.4 (9.7)	56.4 (14.6)
≤65 years, *n* (%)	2486 (57.8)	1507 (51.9)	979 (70.0)
>65 years, *n* (%)	1818 (42.2)	1399 (48.1)	419 (30.0)
Gender, *n* (%)			
Male	2879 (66.9)	1941 (66.8)	938 (67.1)
Female	1425 (33.1)	965 (33.2)	460 (32.9)
Race, *n* (%)			
White	2290 (53.2)	1541 (53.0)	749 (53.6)
Black	191 (4.4)	137 (4.7)	54 (3.9)
Asian	1467 (34.1)	932 (32.1)	535 (38.3)
American Indian/Alaska native	136 (3.2)	111 (3.8)	25 (1.8)
Other	220 (5.1)	185 (6.4)	35 (2.5)

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DAPA – CKD: Baseline Characteristics

Blood pressure (mmHg), mean (SD)			
Systolic	137.1 (17.4)	139.2 (17.3)	132.6 (16.7)
Diastolic	77.5 (10.5)	76.5 (10.1)	79.6 (10.9)
Systolic blood pressure categories, *n* (%)			
>130 mmHg	2762 (64.2)	2033 (70.0)	729 (52.1)
>140 mmHg	1684 (39.1)	1273 (43.8)	411 (29.4)
Mean BMI (kg/m^2)	*n* = 4296	*n* = 2899	*n* = 1397
	29.5	30.3	27.9
HbA_{1c}	*n* = 4284	*n* = 2893	*n* = 1391
%, mean (SD)	7.1 (1.7)	7.8 (1.7)	5.6 (0.4)
mmol/mol, mean (SD)	54 (19)	62 (19)	38 (4)
Haemoglobin (g/L), mean (SD)	*n* = 4278	*n* = 2892	*n* = 1386
	128.3 (18.1)	125.9 (17.9)	133.1 (17.6)

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DAPA – CKD: Baseline Characteristics

Serum creatinine (mg/dL), mean (SD)	1.7 (0.5)	1.6 (0.5)	1.8 (0.5)
eGFR (mL/min/1.73 m^2), mean (SD)	43.1 (12.4)	43.8 (12.6)	41.7 (11.7)
eGFR categories(mL/min/1.73 m^2), *n* (%)			
≥60	454 (10.5)	348 (12.0)	106 (7.6)
45–59	1328 (30.9)	918 (31.6)	410 (29.3)
30–44	1898 (44.1)	1239 (42.6)	659 (47.1)
<30	624 (14.5)	401 (13.8)	223 (16.0)
Baseline UACR (mg/g), median	949.3	1016.5	861.0
Baseline median UACR categories, *n* (%)			
<30 mg/g (Stage A1)	1 (0.0)	1 (0.0)	0 (0.0)
30–300 mg/g (Stage A2)	444 (10.3)	308 (10.6)	136 (9.7)
>300 mg/g (Stage A3)	3859 (89.7)	2597 (89.4)	1262 (90.3)

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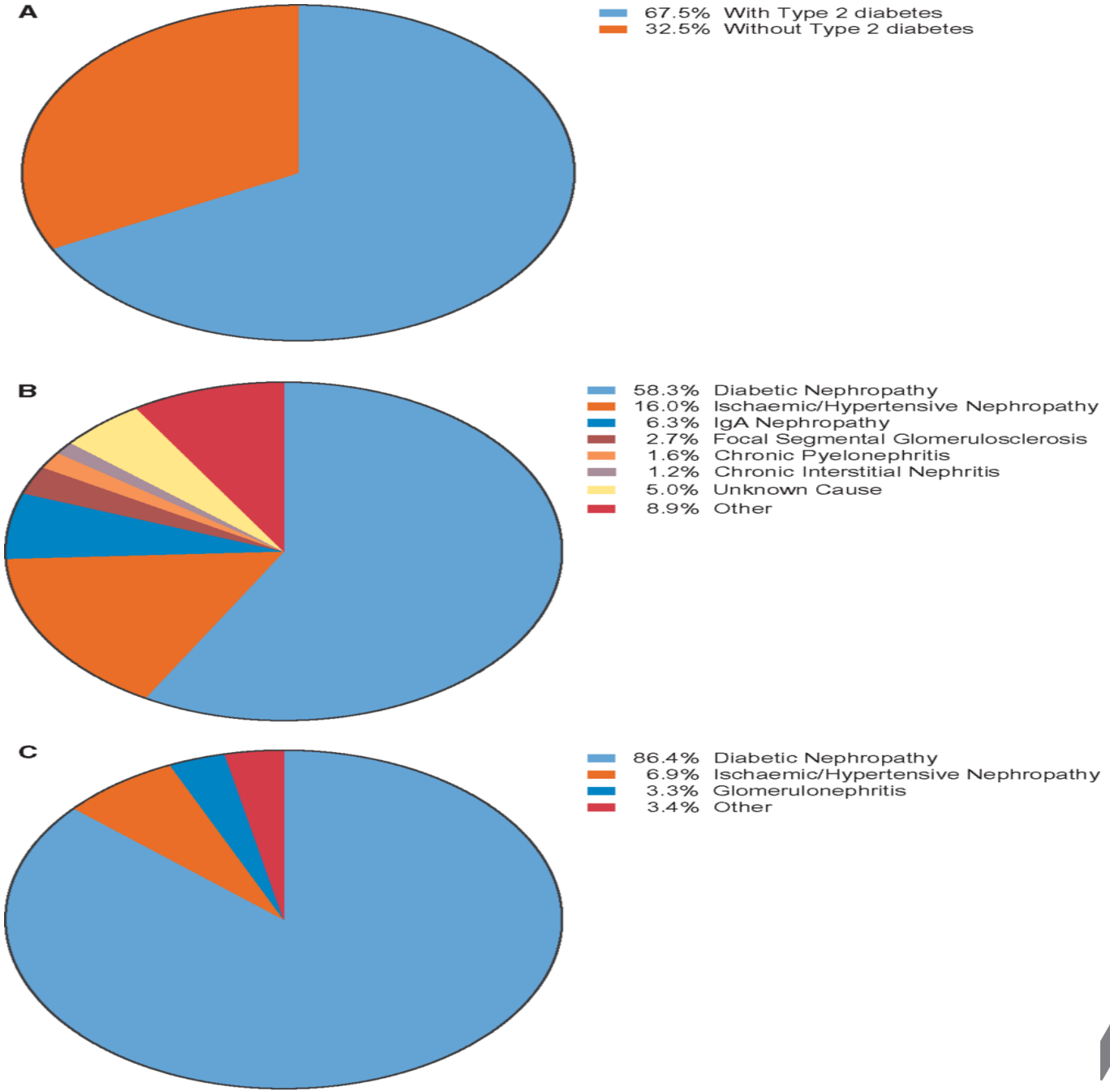
Baseline Characteristics DAPA-CKD



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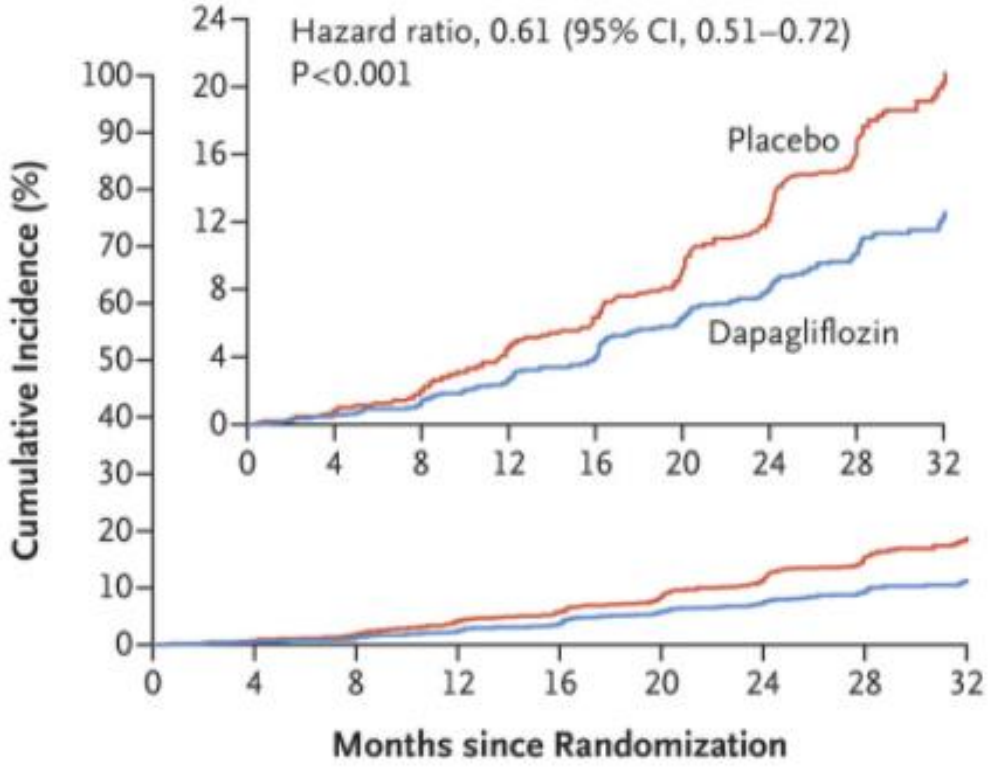
DAPA – CKD

Primary Composite Outcome



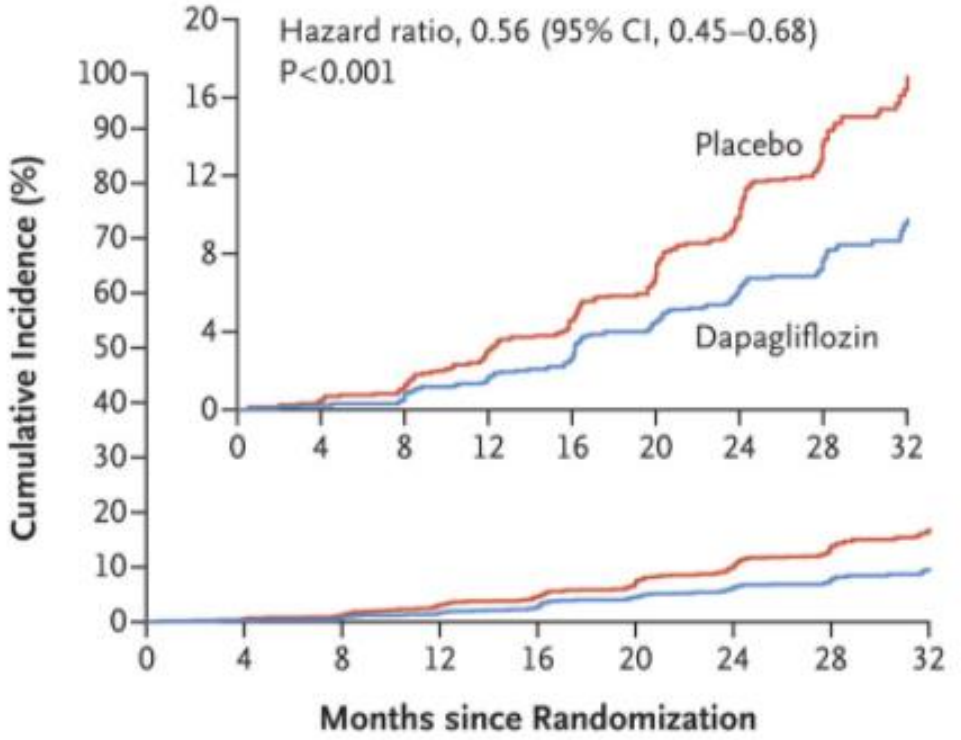
No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

Heerspink et al. Dapagliflozin in patients with chronic kidney disease. NEJM, 2020

DAPA – CKD

Secondary Outcome



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DAPA – CKD
Primary and Secondary Outcomes

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	*events/100 patient-yr*		
Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)	NA
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)	NA
Estimated GFR of <15 ml/min/1.73 m^2	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—	NA
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—	NA
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004

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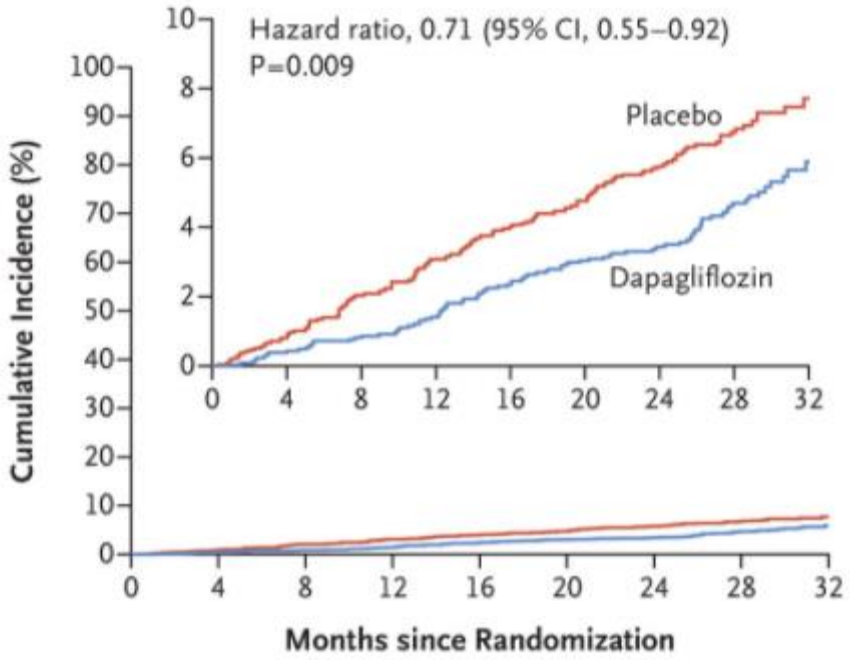
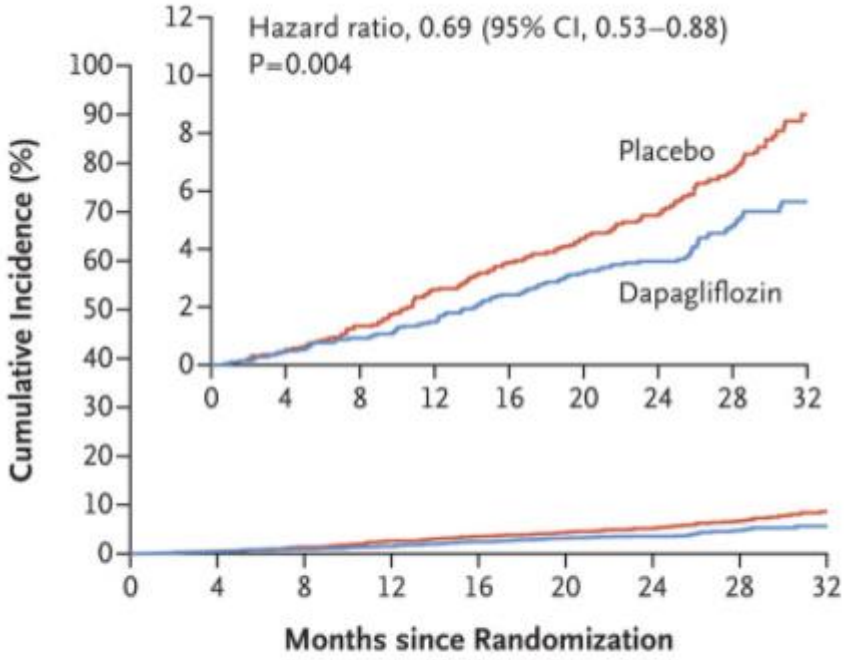
DAPA – CKD
CV and Death Outcomes

Composite of Death from Cardiovascular Cause or Hospitalization for Heart Failure



No. at Risk									
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384

Death from any cause



No. at Risk									
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398

Heerspink et al. Dapagliflozin in patients with chronic kidney disease. NEJM, 2020

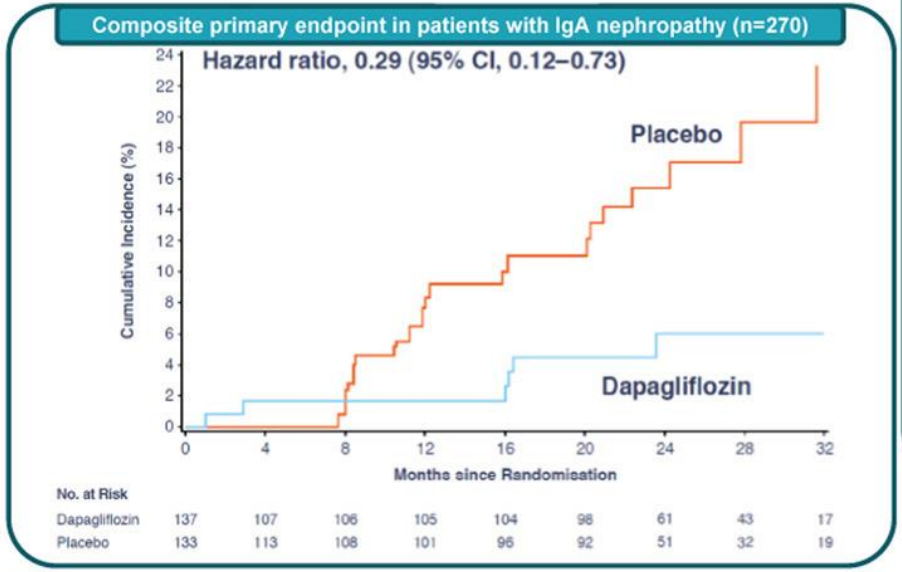
DAPA – CKD & IgA Nephropathy

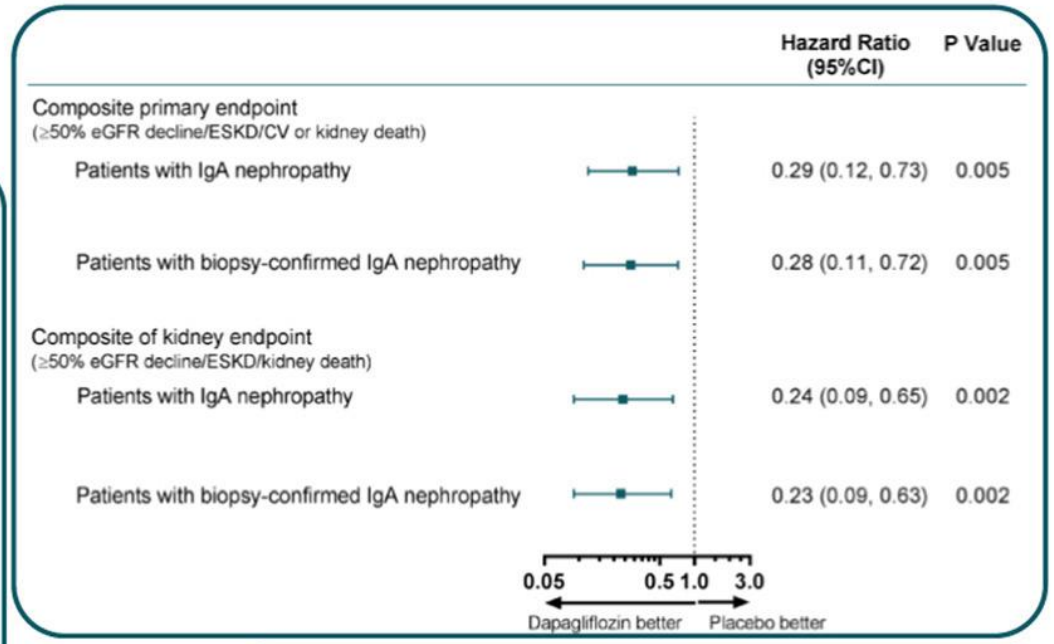
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**





IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

kidney INTERNATIONAL ISN

Wheeler et al, 2021

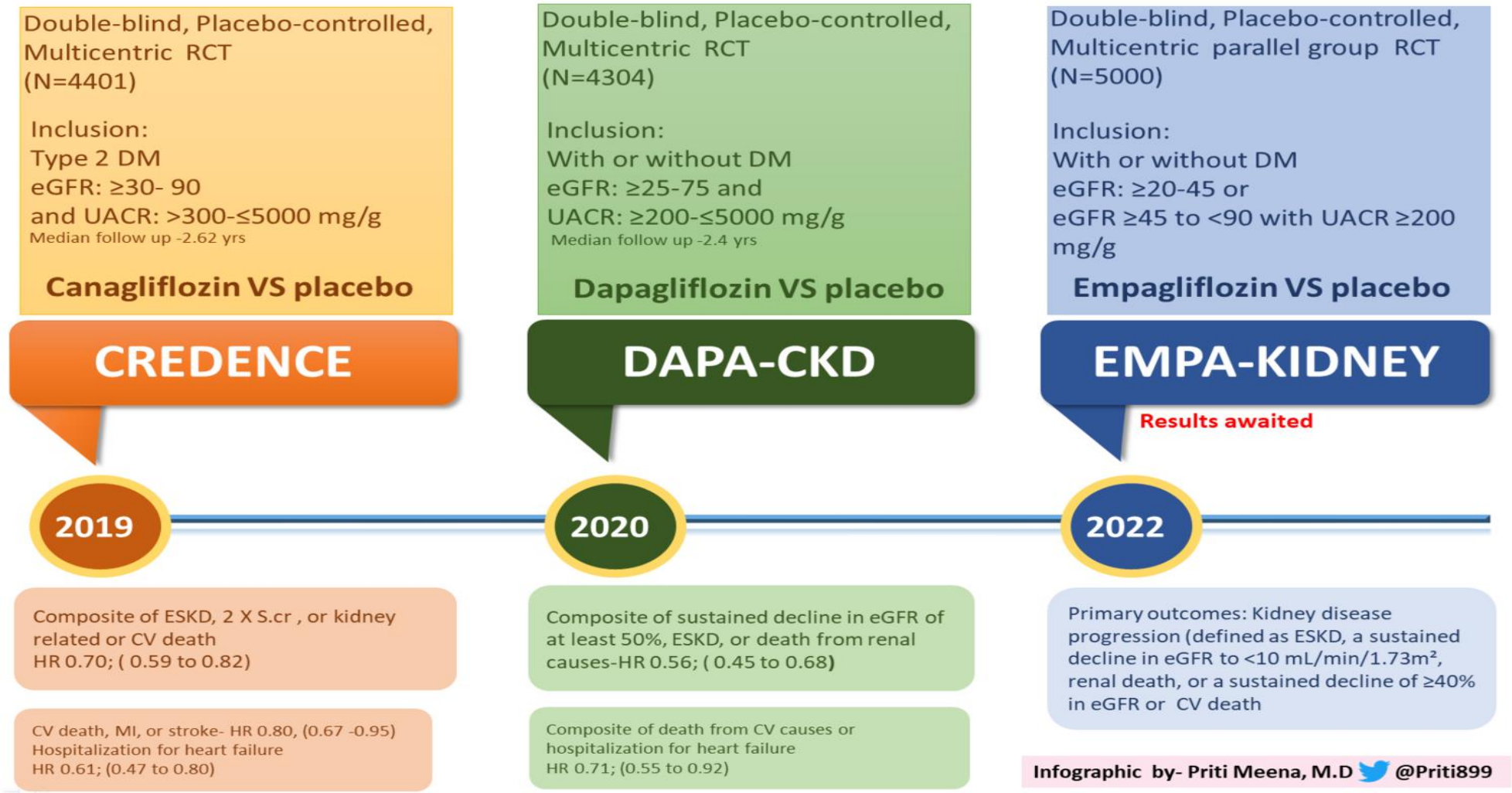
ACOi

DAPA – CKD vs. CREDENCE

- Credence recruited patients with T2DM and CKD with eGR>30 ml/min/1.73m2
- DAPA-CKD included CKD patients with and without T2DM
  - 32.5% of patients with CKD did not have T2DM
  - 14.5% patients had an eGFR below 30 ml/min/1.73 m2

Wheeler et al, NDT 2020

Is This A Class Effect ?



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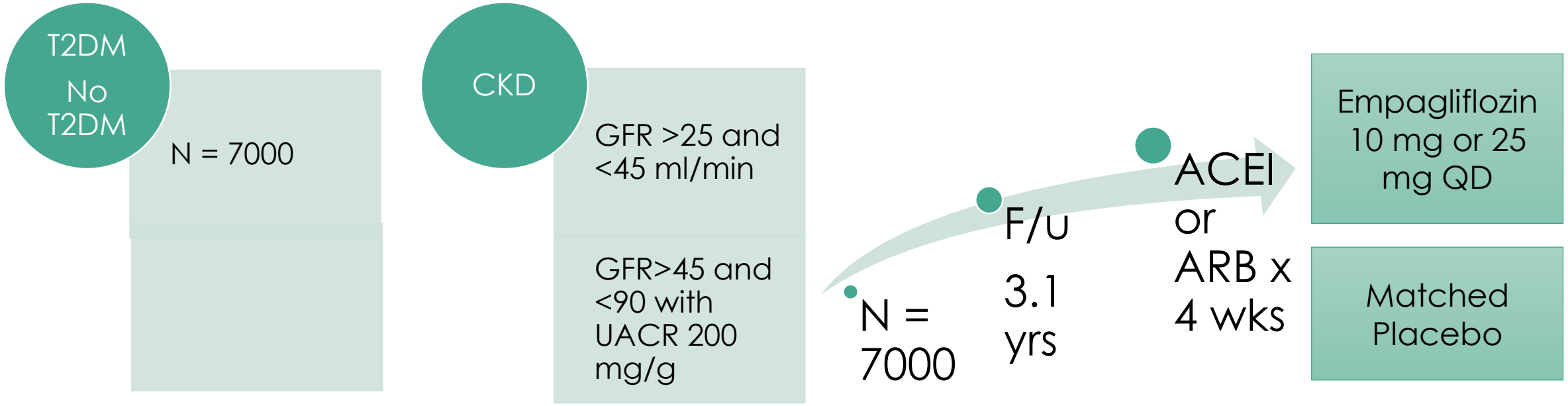
EMPA-KIDNEY



The composite primary outcome:

-Time to first occurrence of (i) kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or (ii) Cardiovascular death

Is it appropriate to generalize the results to all patients with CKD?

- DAPA-CKD enrolled patients with proteinuria.
- Non-proteinuric CKD, notably polycystic kidney disease was excluded.
- Inflammatory glomerulonephritis were also excluded: Lupus and vasculitis. No reason to think SGLT2i have any role here, yet

How low is too low for eGFR?

- Published data from clinical trials report empaglifozin initiation down to GFR 30 (EMPAREG); canaglifozin down to GFR 30 (CREDENCE) and now dapaglifozin down to 25 (DAPA-CKD).
- Both in CREDENCE and in DAPACKD, the drugs were continued down to dialysis - and hence this practice definitely has support.

DAPA – CKD Summary

- 32.5% of patients with CKD did not have T2DM
- 14.5% of patients had a eGFR <30 mL/min/1.73 m2
- There was a 29% relative risk reduction for the composite of death from CV causes or hospitalization for heart failure
- In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression
- Post-hoc analysis of dapagliflozin in patients with low magnesium levels resulted in potential improvement in hypomagnesmia

Summary of Trial Data on SGLT2 Inhibitors

- The Canagliflozin-and-Renal-Events-in-Diabetes-with-Established-Nephropathy-Clinical-Evaluation (CREDENCE) study, showed that canagliflozin substantially reduced the risk of doubling of SCr, end-stage kidney disease (ESKD), or death from renal or cardiovascular causes in 4401 patients with diabetic CKD compared with placebo
- The Study-to-Evaluate-the-Effect-of-Dapagliflozin-on-Renal-Outcomes-and-Cardiovascular-Mortality-in-Patients-With-Chronic-Kidney-Disease (DAPA-CKD), including 2510 patients with diabetic and 1803 with nondiabetic CKD, also showed an impressive reduction in the risk of ≥50% decline in eGFR, ESKD, or death from renal or cardiovascular causes.

Other SGLT2 Inhibitor Benefits

- SGLT2 inhibitors have shown reductions in HbA1c levels (ranges from -0.25 to -0.75% change from baseline)
- SGLT2 inhibitors are also known to reduce blood pressure and weight
- SGLT2 inhibitors have a role in treating IgA nephropathy (as seen by the use of Canagliflozin)
- Hypomagnesemia has also known to have improved with SGLT2i use
- Studies indicate that SGLT2 inhibitors in addition to routine care, can help with sodium retention in patients with SIADH

A Word on GLP-1 Agents and Indications

GLP-1 RA: Study name	N	Median F/u (yrs)	% with CV disease*	% of statin use	Baseline HbA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	7.70%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	8.70%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	8.70%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.10%	74%	8.00%	31.8	0.91 (0.83 to 1.00)	0.06
Dulaglutide: REWIND	9901	5.4	31.50%	66%	7.20%	32.3	0.88 (0.79 to 0.99)	0.026
Semaglutide Oral: PIONEER 6	3183	1.3	84.70%	85%	8.20%	32.3	0.79 (0.57 to 1.11)	0.17

Clinical Use of SGLT2 Inhibitors

- Can be used as adjunct to diet/exercise, metformin and/or other oral medications or insulin for management of T2DM
  - Consider dose reduction of other anti-hyperglycemic agents with well controlled T2DM.
  - 50% oral agent dose or 10-20% pre-meal insulin dose should be considered once SGLT2i are added with well controlled T2DM
- The intravascular volume depletion may result in a reduced blood pressure or dizziness, consider dose reduction of other anti-hypertensives or diuretic agents

Clinical Use of SGLT2 Inhibitors

- A drop in eGFR is expected and should stabilize over 3-4 weeks, can consider re-assessing renal function at 4 weeks after initiating this agent
- SGLT2 inhibitors are safe and effective for as low as GFR 20 ml/min, though caution is advised for GFR 20-30 ml/min
- Continue SGLT2 inhibitor until the onset of dialysis
- Be mindful of UTI or genitomycotic infections, and rare risk of euglycemic diabetic ketoacidosis. Although amputations are not likely, can consider avoiding SGLT2 inhibitors in patients with active wounds or peripheral vascular disease

Conclusion

- SGLT2 inhibitors should be considered in all patients with T2DM and CKD
- SGLT2 inhibitors are approved for use in patient without diabetes with CKD and proteinuria
- SGLT2 inhibitors may be used in diuretic resistant cardio-renal syndrome
- SGLT2 inhibitors can be considered for refractory SIADH, hypomagnesemia, and possible kidney stones

Case Study # 1

- A 70 y/o female with T2DM (A1c 9%) with CKD3b and UACR 600 mg/g, h/o CAD with 2 stents, CVA, presents for management of uncontrolled T2DM. She is on Basaglar 20 units QHS and Admelog 8 units TID AC. SMBG ranges from 180-250 with avg BG 210 mg/mL. She is on Lisinopril 10 mg QD, Coreg 25 mg BID, and Atorvastatin 40 mg QHS. Her LDL was 68 at last lab evaluation. What should you suggest at this time?
  - Continue current regimen of basal-bolus insulin
  - Continue current regimen of basal insulin, start continuous glucose monitoring (CGM), and add-on SGLT2 inhibitor
  - Continue current regimen of basal insulin, start continuous glucose monitoring (CGM), and add-on GLP-1 agonist
  - Continue current regimen of basal insulin, start continuous glucose monitoring (CGM), and add-on DPP4 inhibitor

Case Study #2

- 65 y/o male with T2DM (A1c 8%) with CKD4 (eGFR 29), CAD s/p CABG 5 years ago, CHF (EF 40%), retinopathy, neuropathy, presents for management of T2DM. He is on tradjenta 5 mg QD, Lisinopril 40 mg QD, Lasix 40 mg QD, Metoprolol 25 mg BID, and Atorvastatin 40 mg QD. What is your next best recommendation?
  - Stop Tradjenta and start SGLT2 Inhibitor and reduce Lasix
  - Stop Tradjenta and start GLP-1 agonist and reduce Lasix
  - Continue Tradjenta, start SGLT2 inhibitor and reduce Lasix
  - Continue Tradjenta, start GIP-agonist, and reduce Lasix

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