SGLT2 inhibitie bij CKD zonder proteinurie: Is er voldoende bewijs

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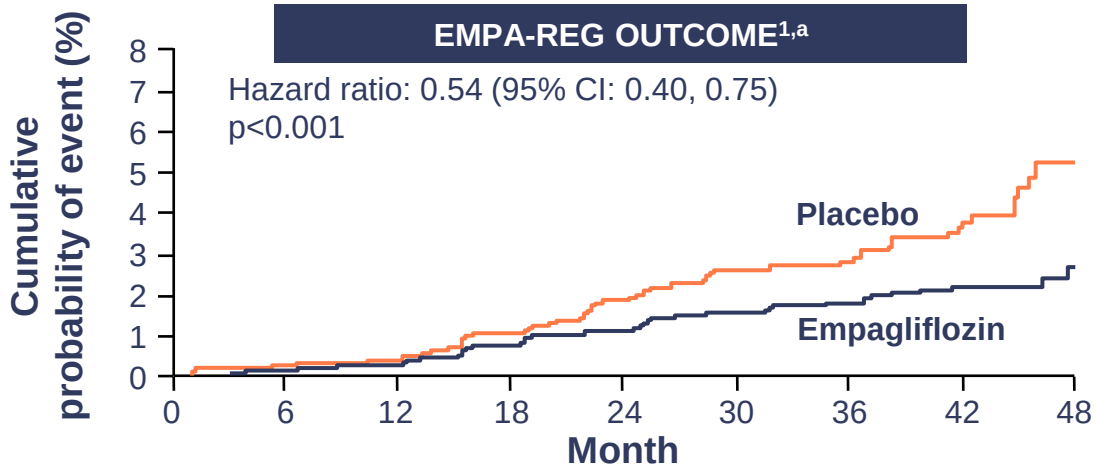
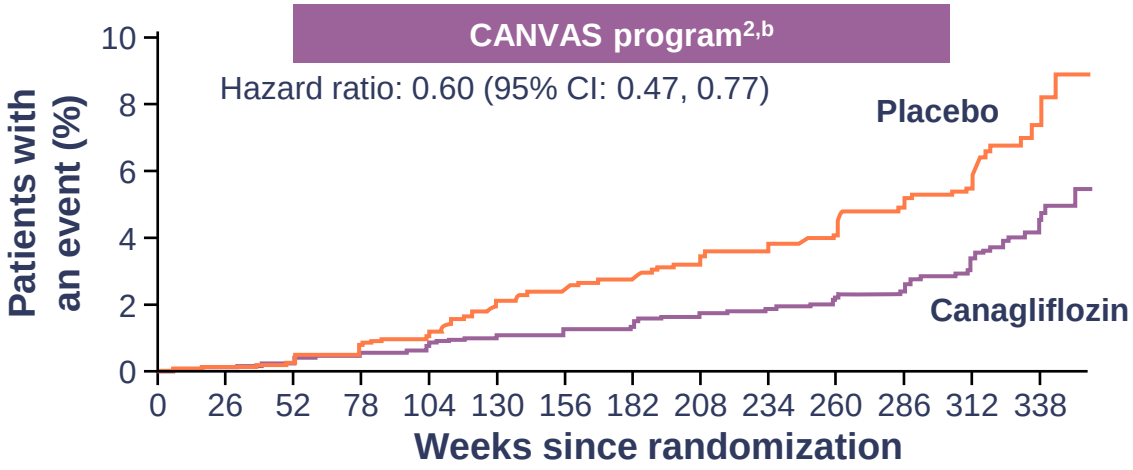
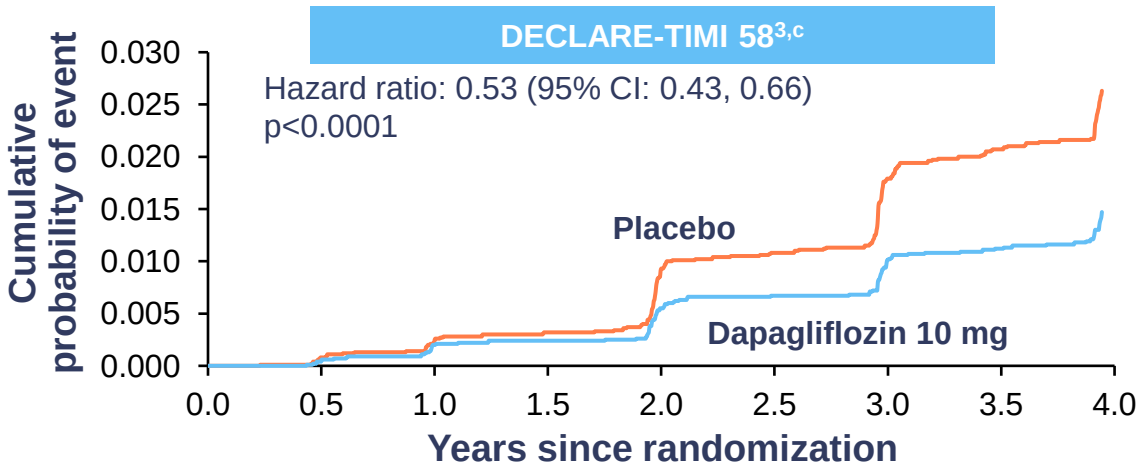
Disclosures

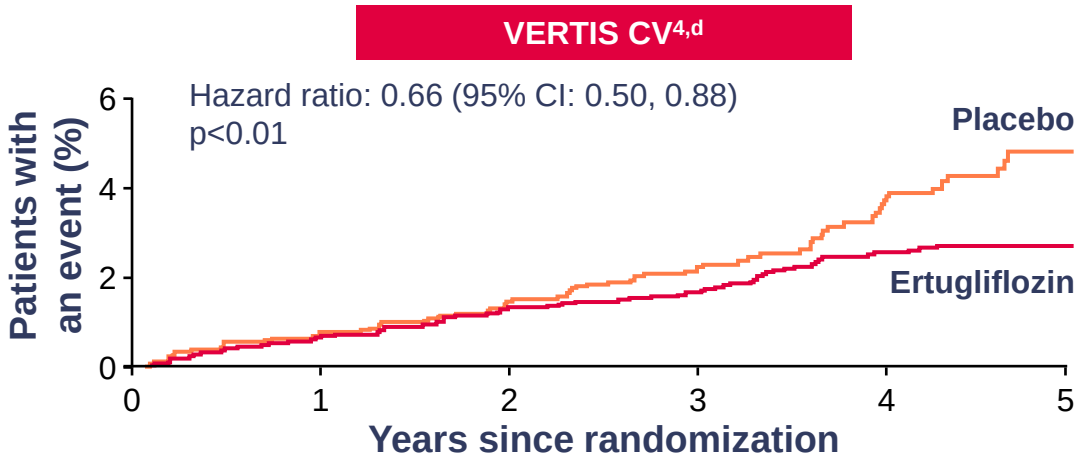
- HJLH is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Eli-Lilly, Gilead, Janssen, Merck, NovoNordisk, and Travere Therapeutics
- He has received research support from AstraZeneca, Boehringer Ingelheim, Janssen and NovoNordisk

SGLT2 inhibitors have demonstrated a class effect in reducing risk of composite kidney disease endpoints in T2D







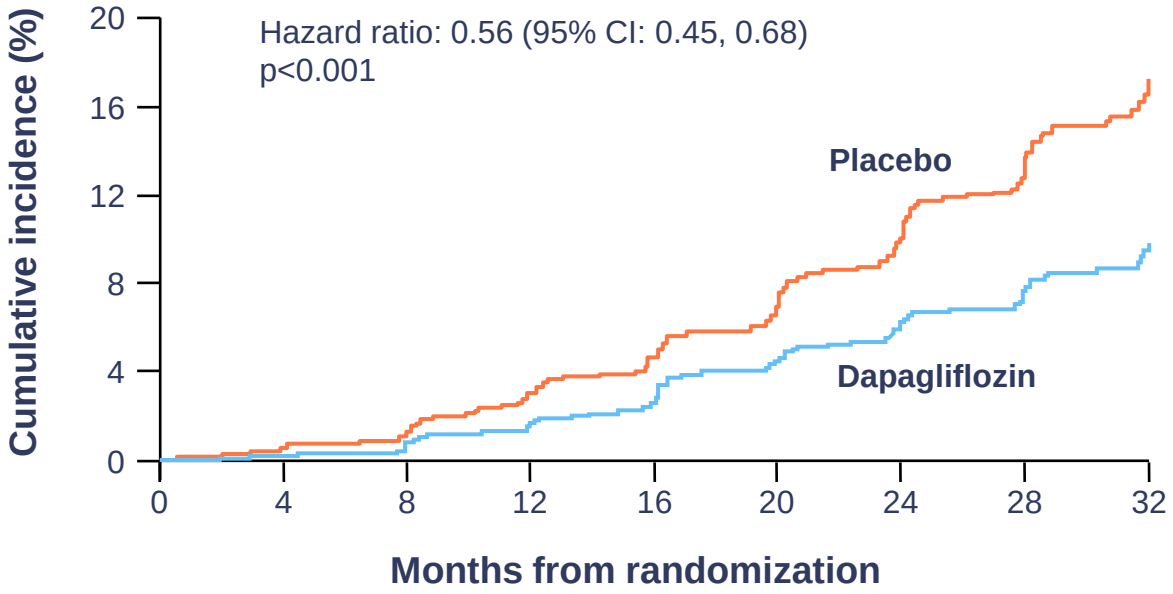


[a]Composite kidney disease endpoint defined as dSCr accompanied by eGFR ≤45 mL/min/1.73 m^2, RRT, or kidney death; [b]40% reduction in eGFR, KRT, or death from kidney causes; [c]eGFR decrease ≥40% to <60 mL/min/1.73 m^2, ESKD, or kidney death; [d]Exploratory endpoint defined as sustained 40% decrease from baseline in eGFR, chronic renal dialysis/transplant, or renal death
CI, confidence interval; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease;
KRT, kidney replacement therapy; RRT, renal replacement therapy; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

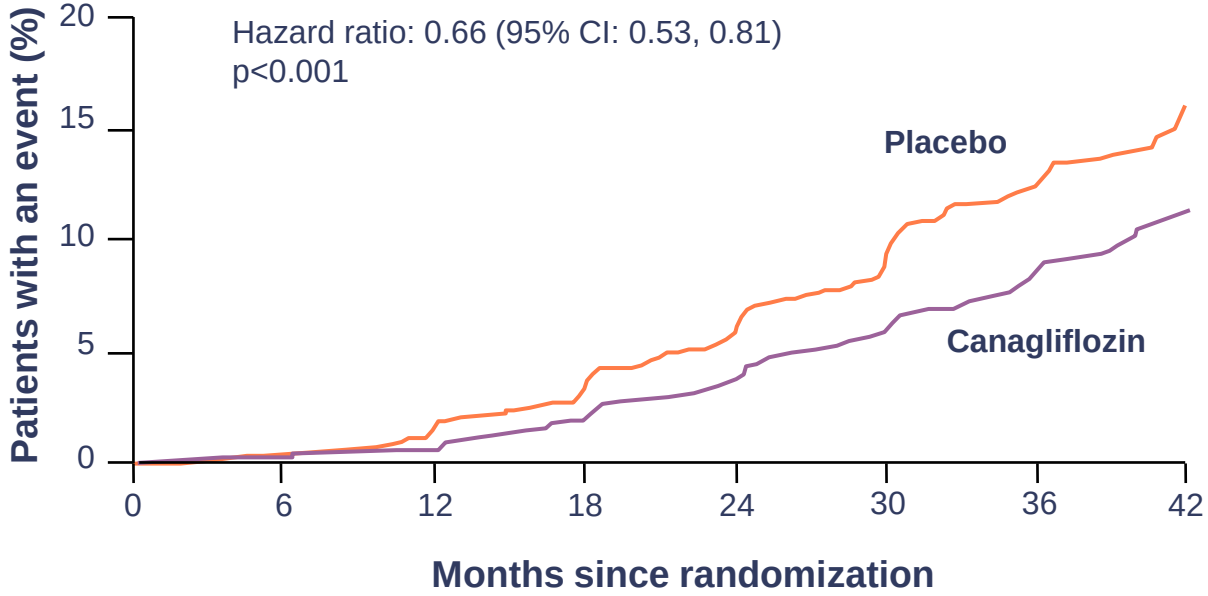
1. Wanner C, et al. *N Engl J Med* 2016;375:323–334; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657;
3. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 4. Cherney DZI, et al. *Diabetologia* 2021;64:1256–1267

SGLT2 inhibitors significantly reduce the risk of composite kidney outcomes in patients with CKD

DAPA-CKD[1a]

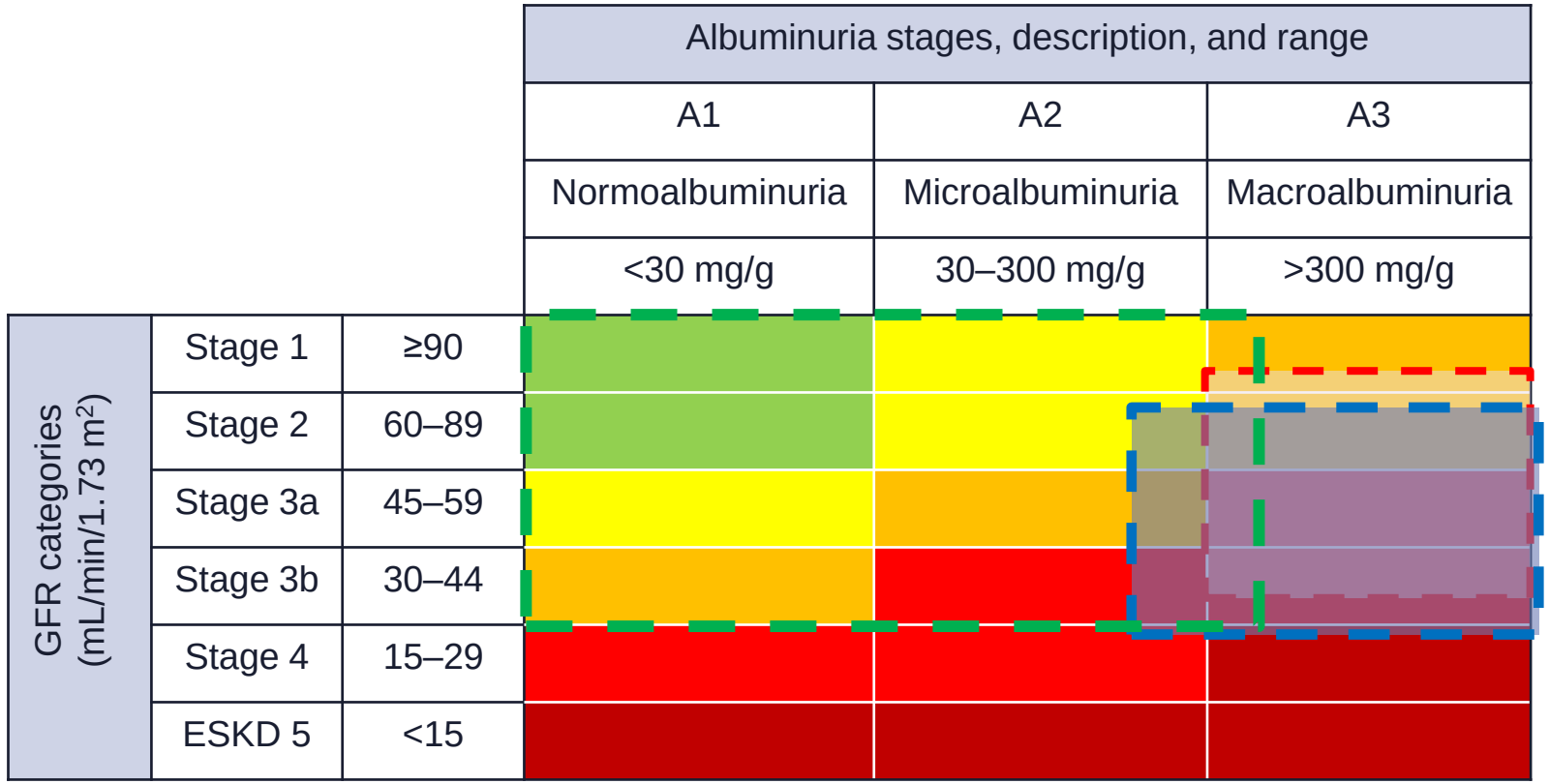


CREDENCE[2b]



[a]Kidney-specific composite outcome of a sustained decline in eGFR of at least 50%, ESKD, or death from renal causes
[b]Kidney-specific composite outcome of ESKD, doubling of serum creatinine level, or renal death
CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SGLT2, sodium–glucose co-transporter 2
1. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 2. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306

Kidney outcome trials with SGLT2 inhibitors address the spectrum of CKD



E=EMPAREG-Outcome; C=CANVAS; D=DECLARE TIMI-58

EMPAREG (T2D and CV)
eGFR ≥30mL/min/1.73 m²

CANVAS (T2D and CV risk)
eGFR ≥30 mL/min/1.73 m²

DECLARE (T2D and CV risk)
Creat Clearance >60 mL/min

VERTIS (T2D and CV)
eGFR>30

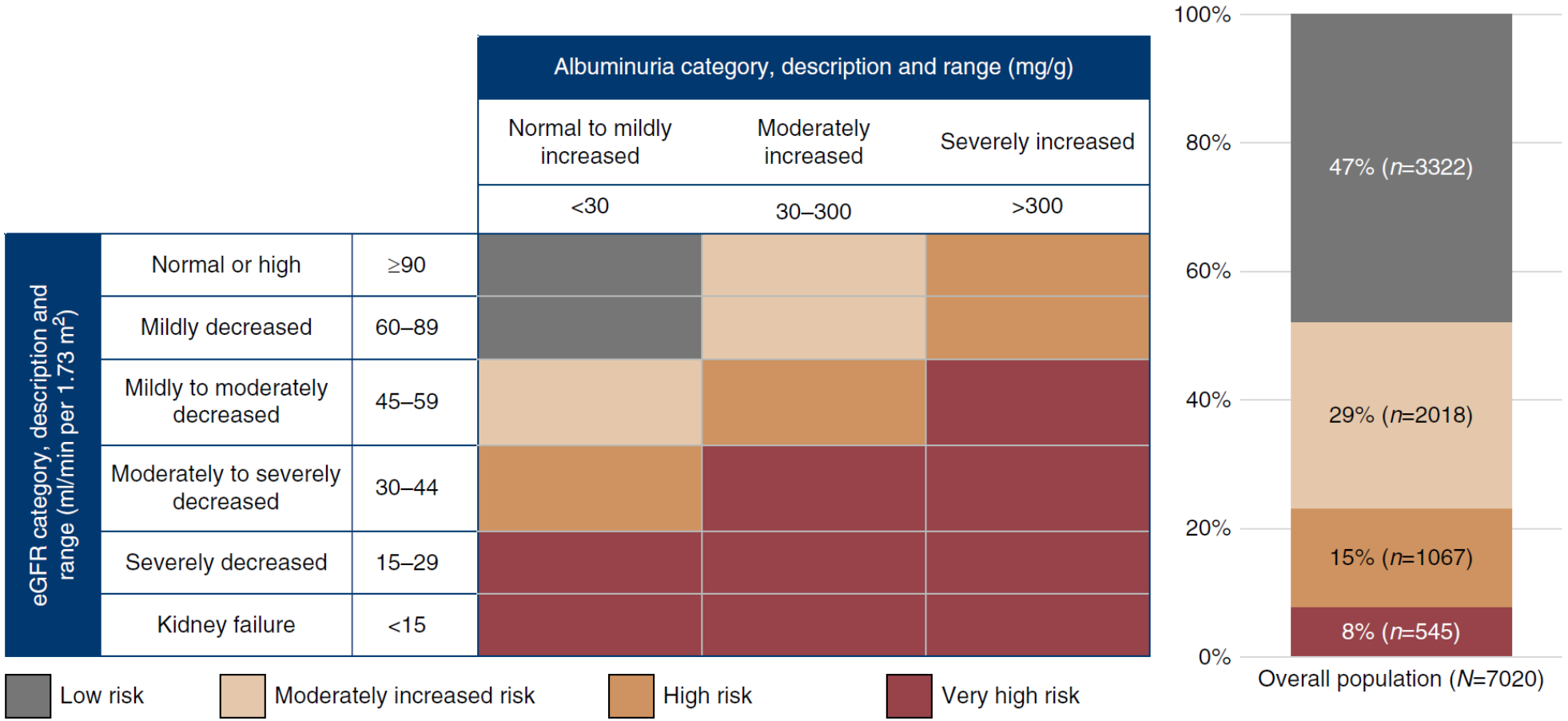
CREDENCE (DKD only)
eGFR ≥30 to <90 mL/min/1.73 m²
and UACR ≥300 mg/g

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

CKD, chronic kidney disease; DKD, diabetic kidney disease, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; SGLT2, sodium–glucose co-transporter 2; UACR, urine albumin:creatinine ratio

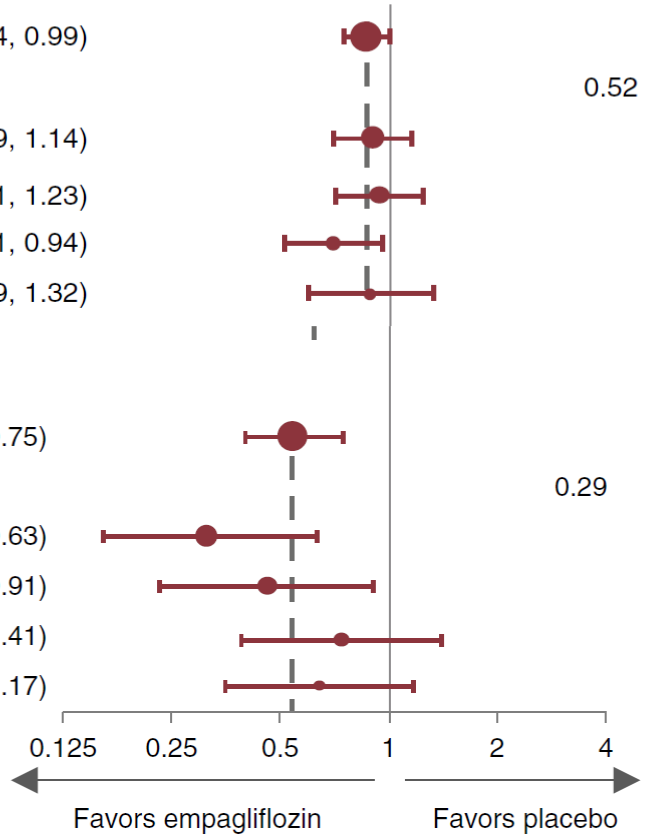
Heerspink HJL, et al. *Nephrol Dial Transplant* 2020;35:274–282

EMPAREG: Proportions of patients by baseline KDIGO Risk



Consistent benefit of SGLT2i across all KDIGO risk stages

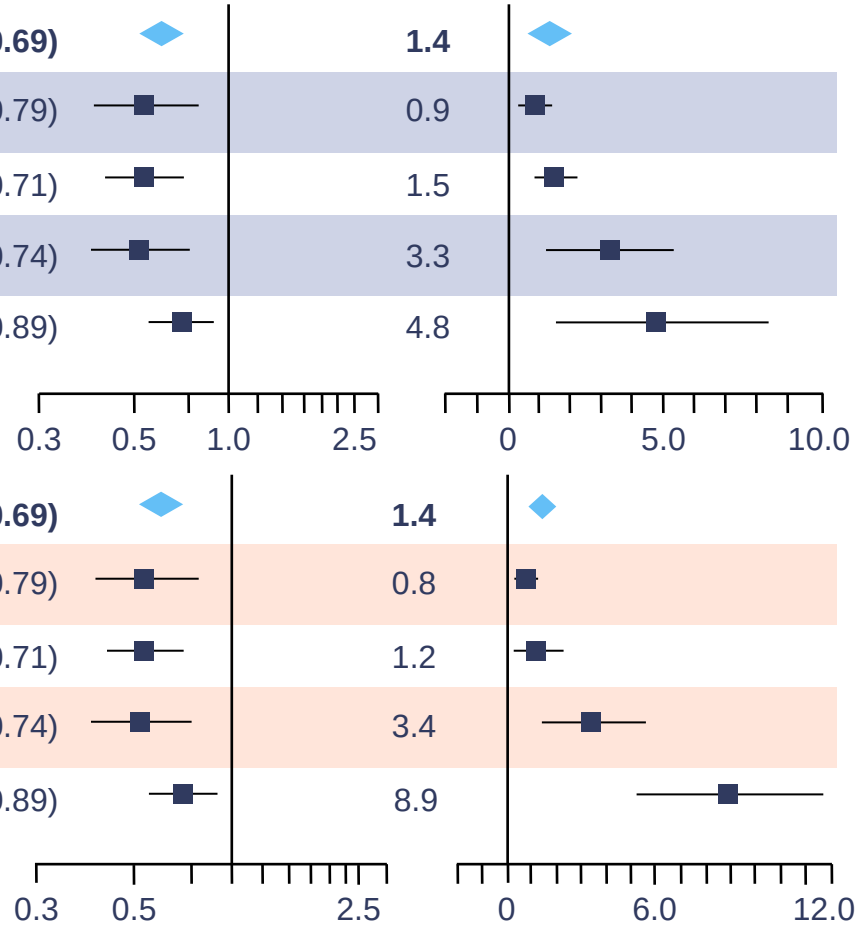
	Empagliflozin	Placebo	Hazard ratio (95% CI)	Hazard ratio (95% CI)	*P*-value for interaction
	n with event/N analyzed (%)				
3-point MACE					
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)		
KDIGO risk categories*					0.52
Low risk	175/2223 (7.9)	97/1099 (8.8)	0.89 (0.69, 1.14)		
Moderately increased risk	146/1343 (10.9)	79/675 (11.7)	0.93 (0.71, 1.23)		
High risk	99/710 (13.9)	69/357 (19.3)	0.69 (0.51, 0.94)		
Very high risk	65/359 (18.1)	37/186 (19.9)	0.88 (0.59, 1.32)		
Doubling of serum creatinine,† initiation of kidney replacement therapy, or death from kidney					
All patients	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)		
KDIGO risk categories*					0.29
Low risk	13/2205 (0.6)	20/1094 (1.8)	0.31 (0.16, 0.63)		
Moderately increased risk	16/1334 (1.2)	17/671 (2.5)	0.46 (0.23, 0.91)		
High risk	25/704 (3.6)	15/356 (4.2)	0.74 (0.39, 1.41)		
Very high risk	24/352 (6.8)	19/186 (10.2)	0.64 (0.35, 1.17)		



Levin et.al. CJASN 2020 1443-43

Relative efficacy and risk difference of dapagliflozin vs placebo on kidney events by eGFR and UACR

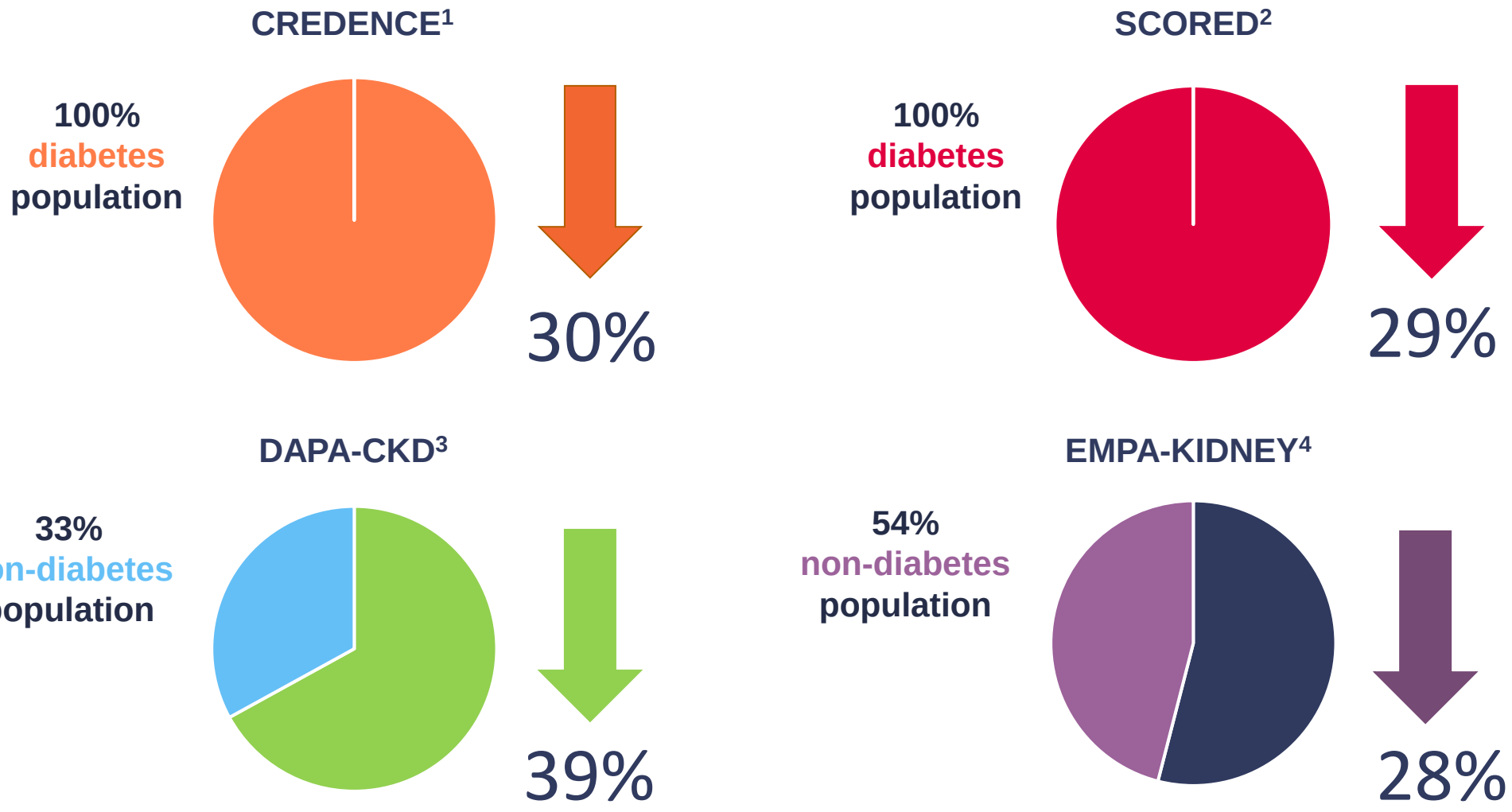
	Event rate n/N (%)			
	Placebo (N=9864)	Dapagliflozin 10 mg (N=9894)	HR (95% CI)	ARD
Kidney events				
Overall	**4.9**	**3.0**	**0.60 (0.52–0.69)**	**1.4**
eGFR ≥90	2.0	1.1	0.54 (0.38–0.79)	0.9
eGFR 60–<90	3.5	1.9	0.54 (0.41–0.71)	1.5
eGFR 45–<60	5.0	9.2	0.52 (0.37–0.74)	3.3
eGFR <45	18.6	13.9	0.71 (0.56–0.89)	4.8
Kidney events				
Overall	**4.9**	**3.0**	**0.60 (0.52–0.69)**	**1.4**
UACR <30	1.6	0.9	0.54 (0.38–0.79)	0.8
UACR 30–<300	3.2	2.0	0.54 (0.41–0.71)	1.2
UACR 300–<1000	7.4	4.0	0.52 (0.37–0.74)	3.4
UACR ≥1000	26.3	17.8	0.71 (0.56–0.89)	8.9



ARD, absolute relative difference; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, urine albumin:creatinine ratio

Moura F, et al. Presented at the European Society of Cardiology 2022. Barcelona, Spain, 26–29 August 2022

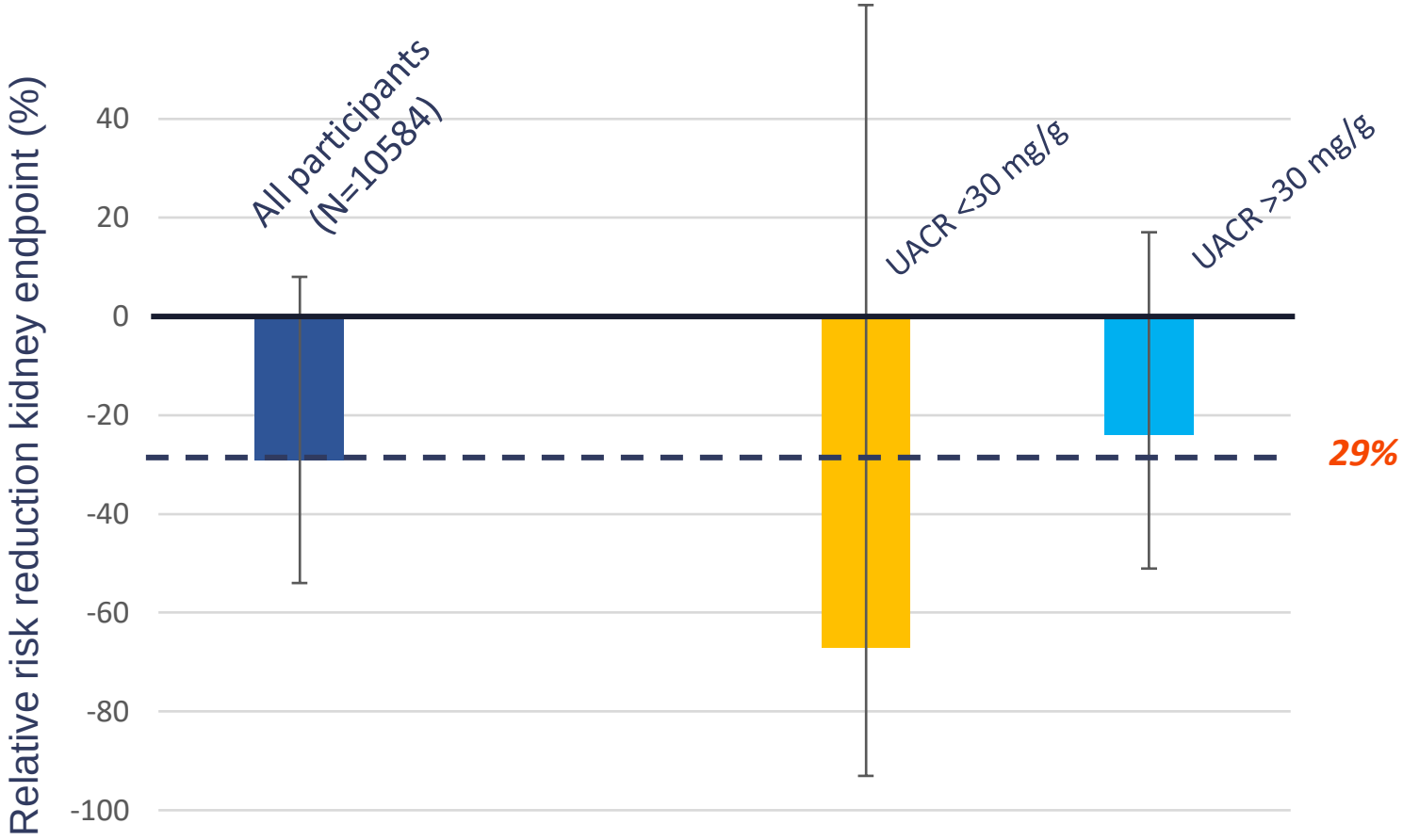
SGLT2 inhibitor trials have recruited patients with CKD with and without diabetes



CKD, chronic kidney disease

1. Perkovic V, et al. *N Engl J Med* 2019;380:2295–306; 2. Bhatt DL, et al. *N Engl J Med* 2021;384:129–139;
3. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 4.EMPA-KIDNEY Collaborative Group. *N Engl J Med* Nov 4. doi: 10.1056/NEJMoa2204233

SCORED: Kidney benefits in participants with type 2 diabetes, eGFR<60 irrespective of baseline albuminuria



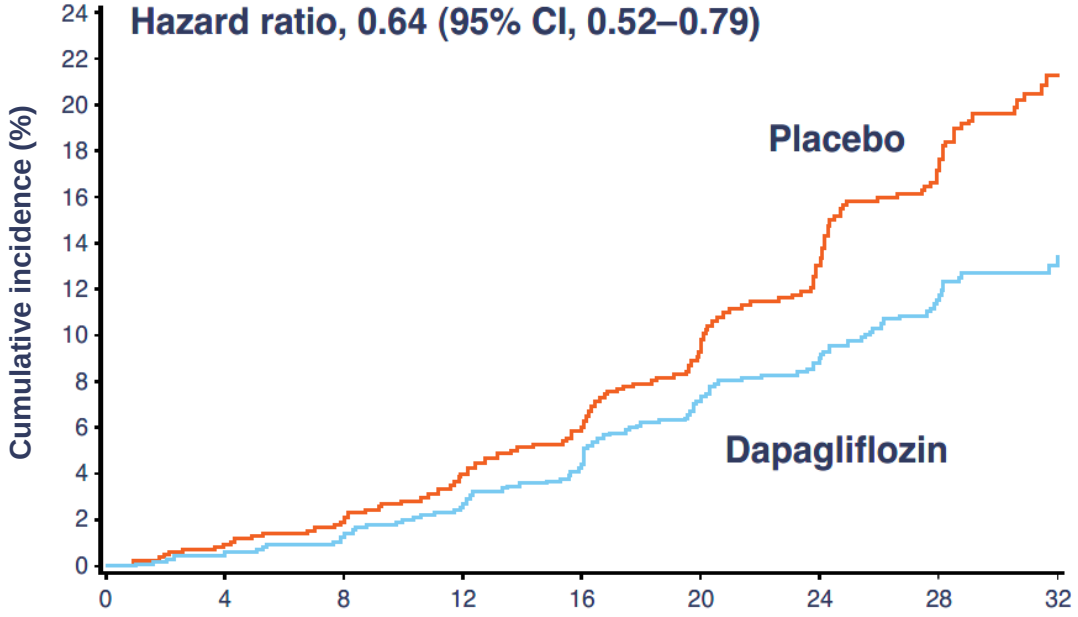
Kidney endpoint defined as 50% eGFR decline, ESKD, death due to kidney failure

Bhatt et.al. New Eng J Med 2020 Nov 16

Primary outcome: participants with and without T2D

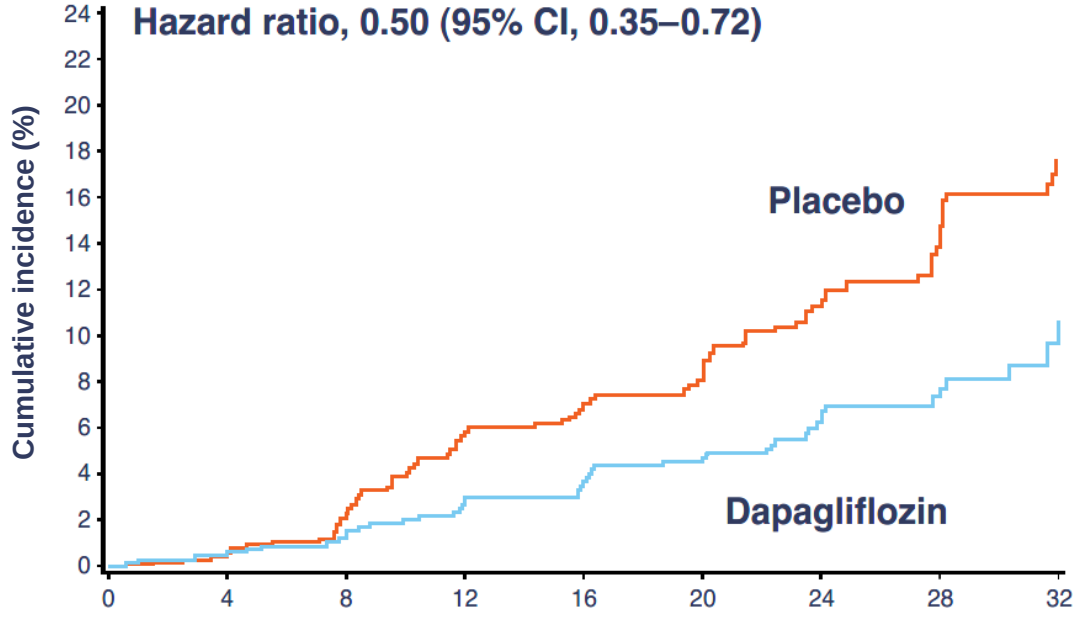
Composite of sustained decline in eGFR of at least 50%, ESKD, or kidney-related or cardiovascular death

With T2D



No. at Risk									
Dapagliflozin	1455	1383	1349	1307	1262	1155	910	580	215
Placebo	1451	1360	1321	1275	1224	1130	868	545	190

Without T2D

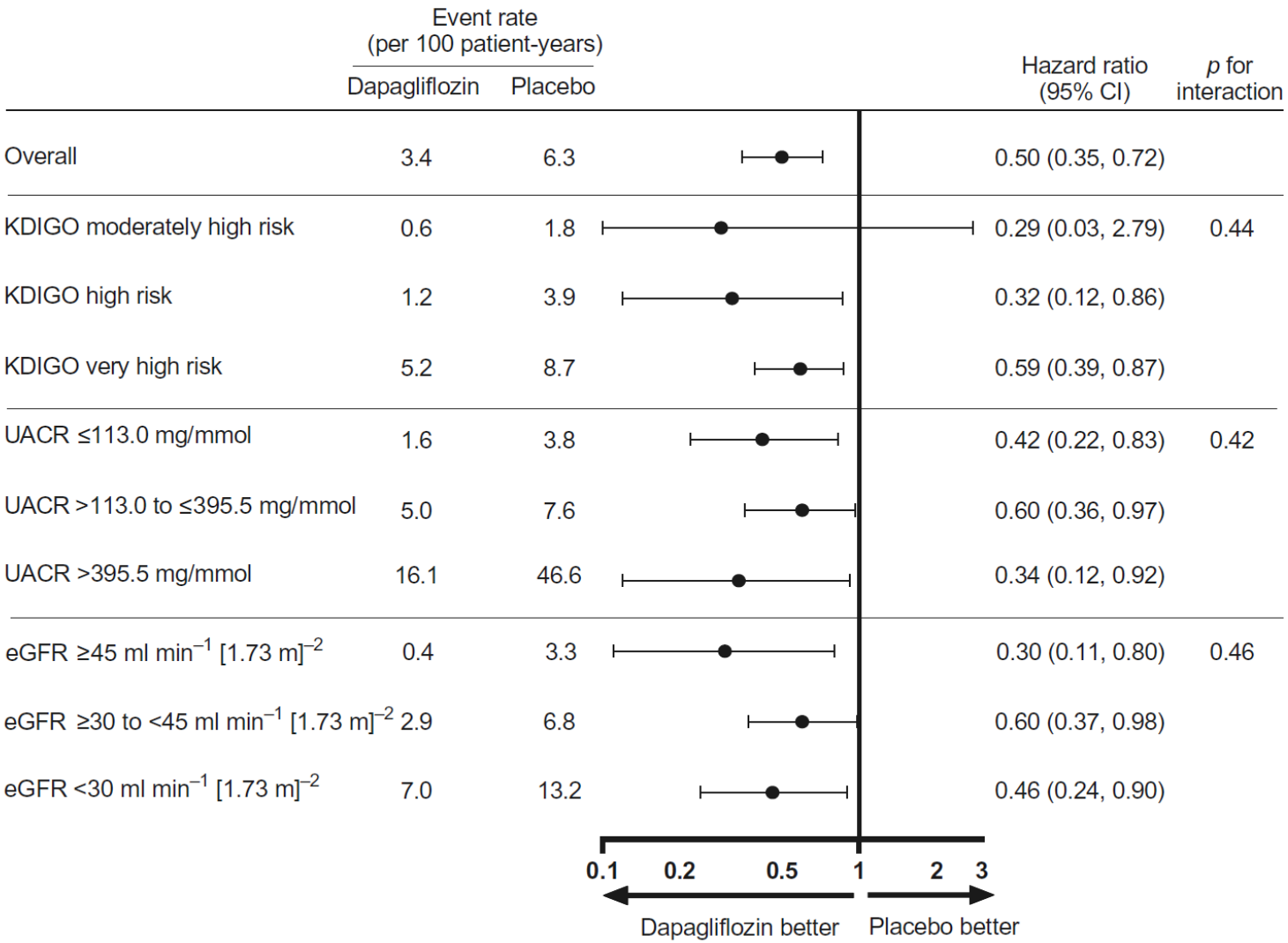


No. at Risk									
Dapagliflozin	697	618	606	591	579	546	378	251	94
Placebo	701	633	615	583	567	534	364	229	80

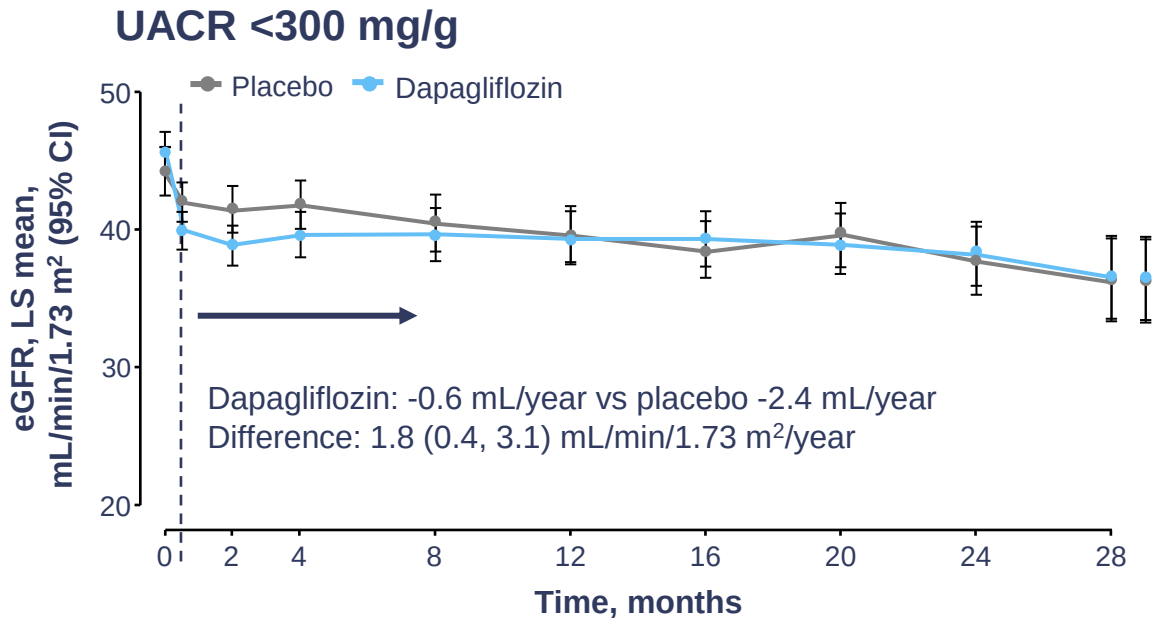
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; T2D, Type 2 diabetes

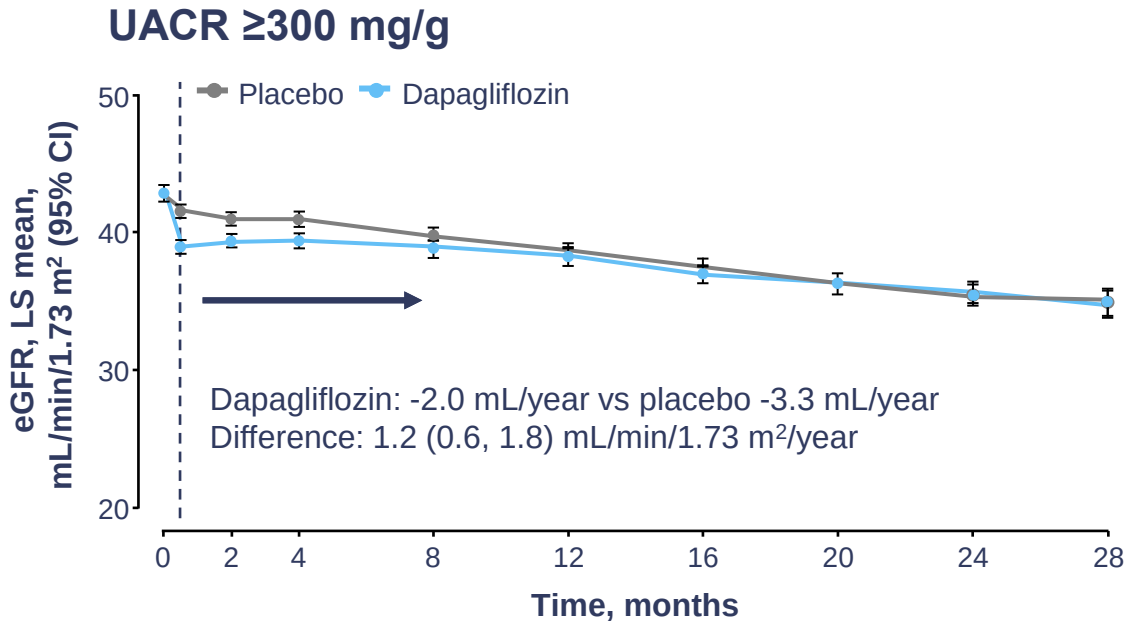
Wheeler DC, et al. *Lancet Diabetes Endocrinol* 2021;9:22–31

DAPA-CKD: Dapagliflozin consistently reduced the risk of kidney failure irrespective of KDIGO risk In patients *without* diabetes



Dapagliflozin reduces long-term eGFR decline in participants *without* diabetes *with* microalbuminuria

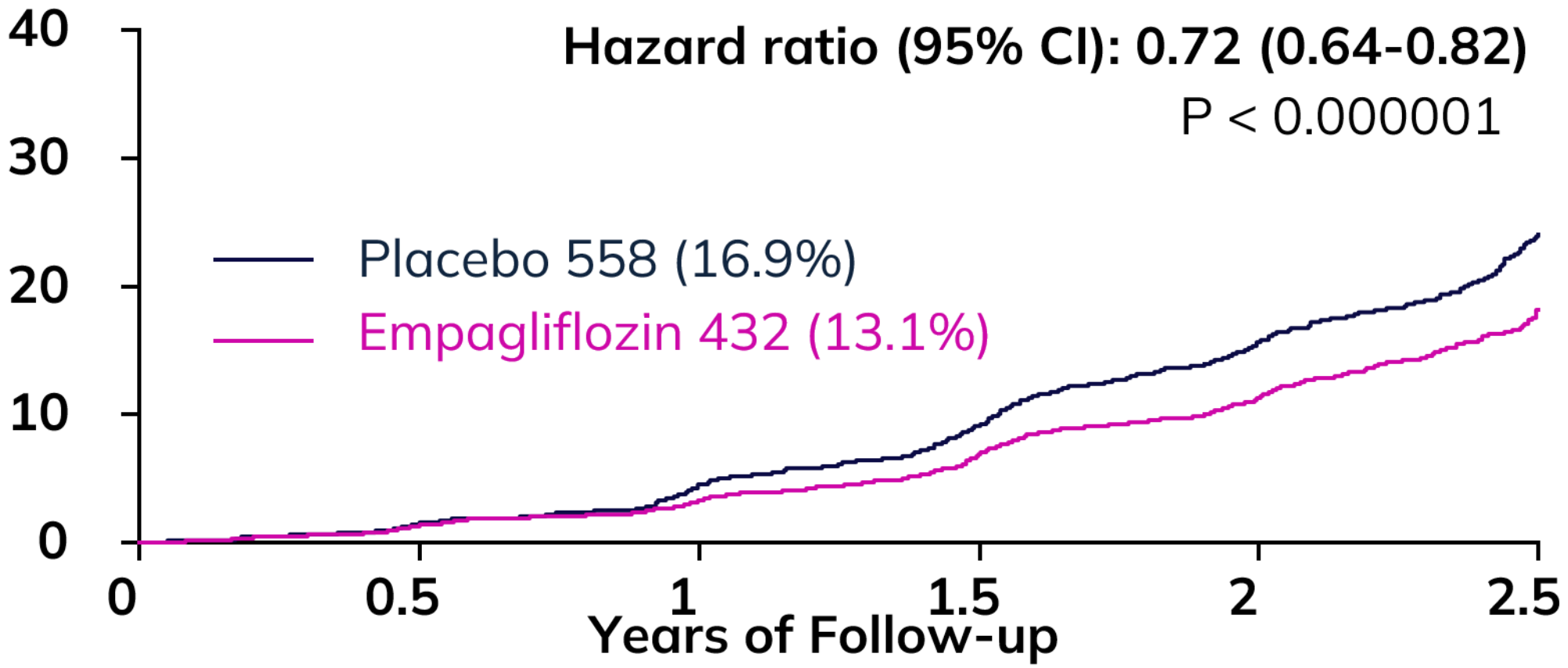




CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; UACR, urine albumin:creatinine ratio

Heerspink HJL, et al. *CJASN* 2022;17(9):CJN.07290622

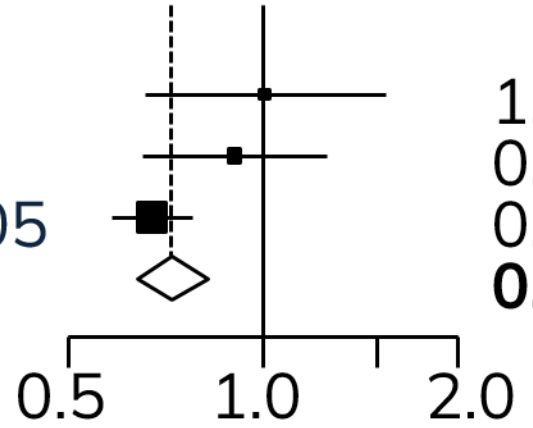
EMPA-Kidney: Primary Composite Outcome
(*N=6609 participants / 54% without diabetes*)



Herrington et.al. New Engl J Med 2022

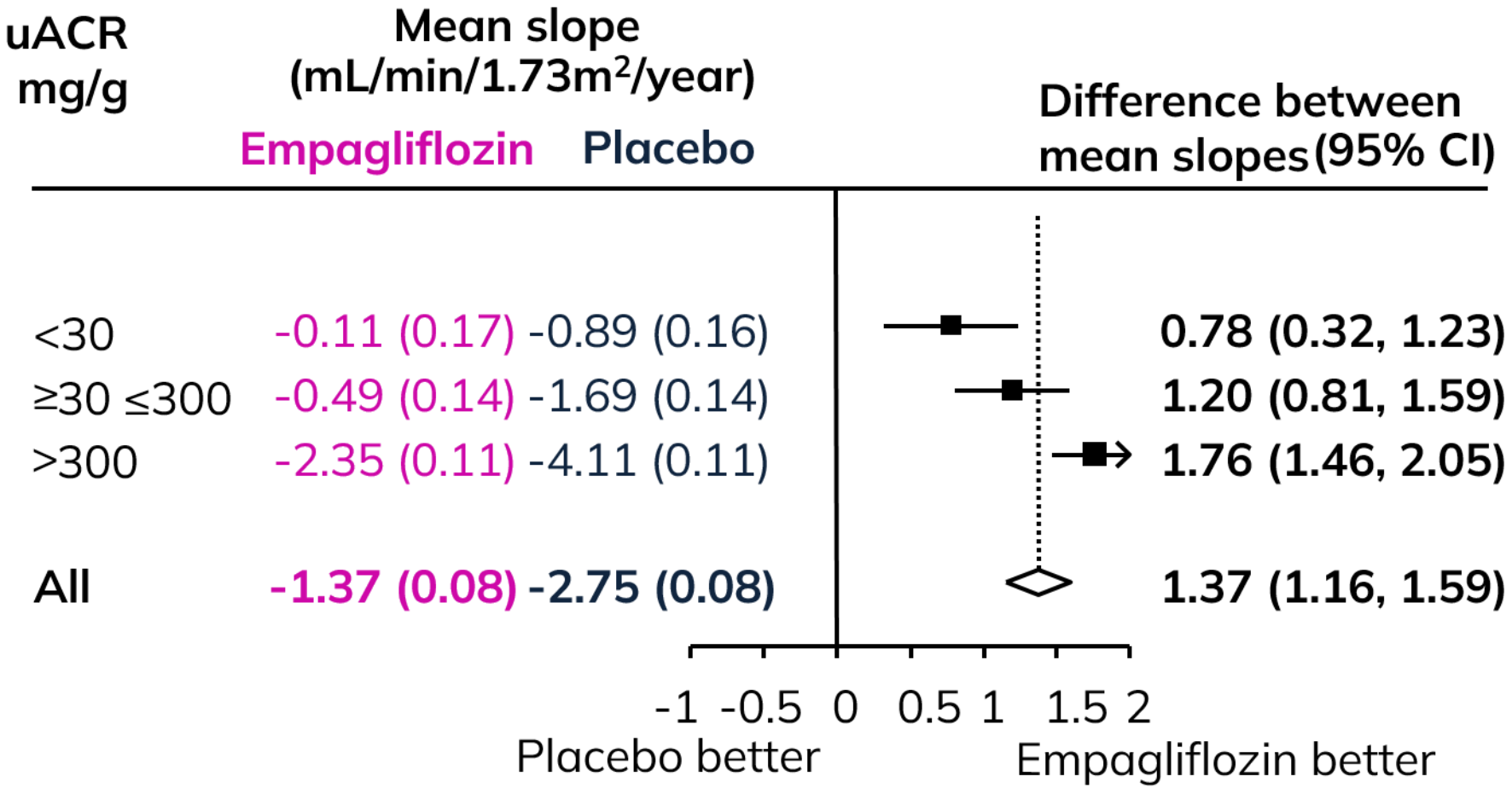
Primary outcome by albuminuria

uACR mg/g		No. of events / participants: Empagliflozin	Placebo	Hazard Ratio (95% CI)
<30	(A1)	42/665	42/663	1.01 (0.66–1.55)
≥30 ≤300	(A2)	67/927	78/937	0.91 (0.65–1.26)
>300	(A3)	323/1712	438/1705	0.67 (0.58–0.78)
All participants				**0.72 (0.64–0.82)**



Trend P value= 0.02

Chronic eGFR slopes by albuminuria



Prespecified exploratory analyses

SGLT2 inhibitie bij CKD zonder proteinurie:
Is er voldoende bewijs?

JA!

In deze PRO-CON discussie verdedig ik de PRO argumenten; de werkelijkheid is altijd genuanceerder dan deze eenvoudige presentatie