DAPA-CKD

AstraZeneca

Ad uso esclusivo del Medical Affairs

DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

DAPACKD

Objective To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a stable dose of an ACEi or ARB

Key Inclusion Criteria
- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria
- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

1:1 Double-blind

- Dapagliflozin 10 mg + standard of care
- Placebo + standard of care

4304 Randomized
Median follow-up 2.4 years

End Points

Primary Outcome
Composite of sustained ≥50% eGFR decline, ESKD[a], renal or CV death

Secondary Outcomes
- Composite of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

DAPA-CKD enrolled a diverse population of patients with CKD, including various etiologies

eGFR range[2,b]
25-75 mL/min/1.73 m²
- **eGFR ≥45: 41%**
- **eGFR <45: 59%**

UACR range[1]
≥200 to ≤5000 mg/g

DAPA therapy could continue following dialysis initiation[3,4,c]

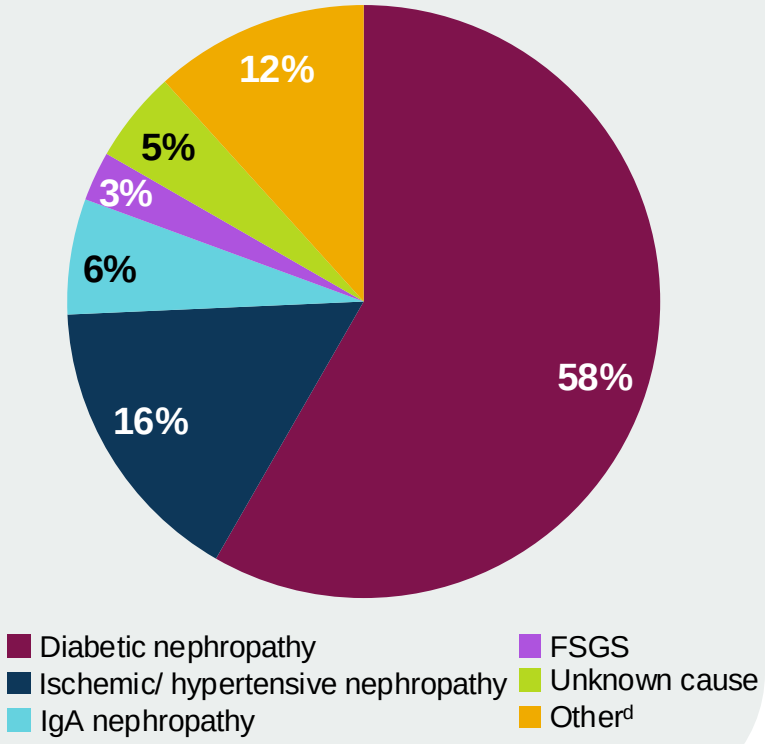
Mean eGFR[1]
43 mL/min/1.73 m²

Median uACR 965 mg/g in **dapagliflozin** and **934mg/g** in **placebo** group

Medical Hystory:
- Type 2 diabetes 67%
- CVD 37%
- HF 10%

ACEi or ARB : 97%

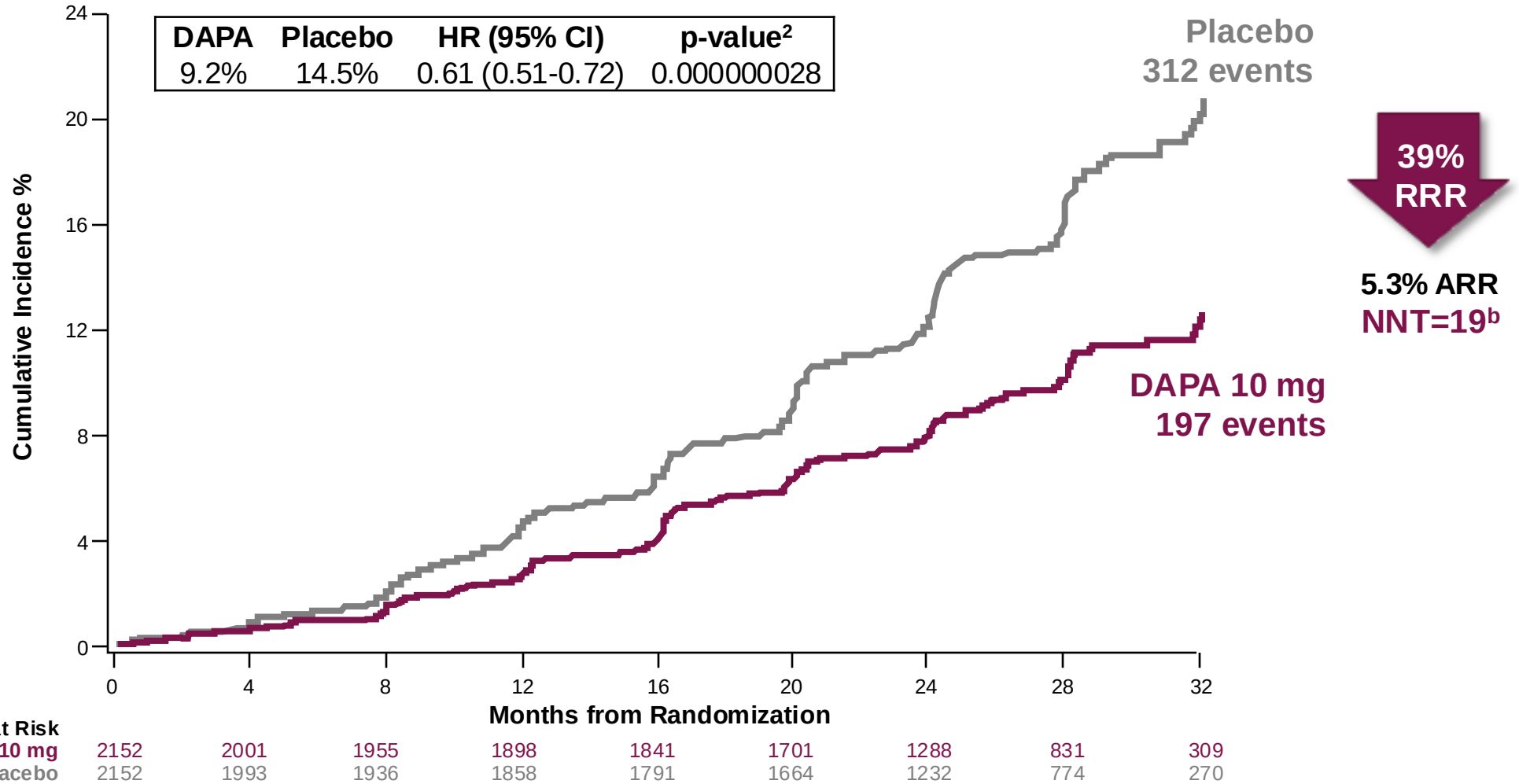
Cause of kidney disease[2]



[a]All patients were required to be on a stable dose of an ACE inhibitor or ARB for at least 4 weeks before screening, if not medically contraindicated. Patients with T1D, polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody-associated vasculitis were excluded; [b]Patients were permitted to continue with dapagliflozin therapy if eGFR fell to <25 mL/min/1.73 m² over the course of the study; [c]At the investigators discretion; [d]'Other' included patients with chronic pyelonephritis, chronic interstitial nephritis, and other causes.

1. Heerspink HJL et al. *N Engl J Med*. 2020:383(15):1436-1446; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35(10):1700-1711; 3. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35(2):274-282; 4. Heerspink HJL et al. *Eur Heart J*. 2021;42(13):1216-1227.

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a,1]



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[3]; [b]95% CI, 15 to 27.

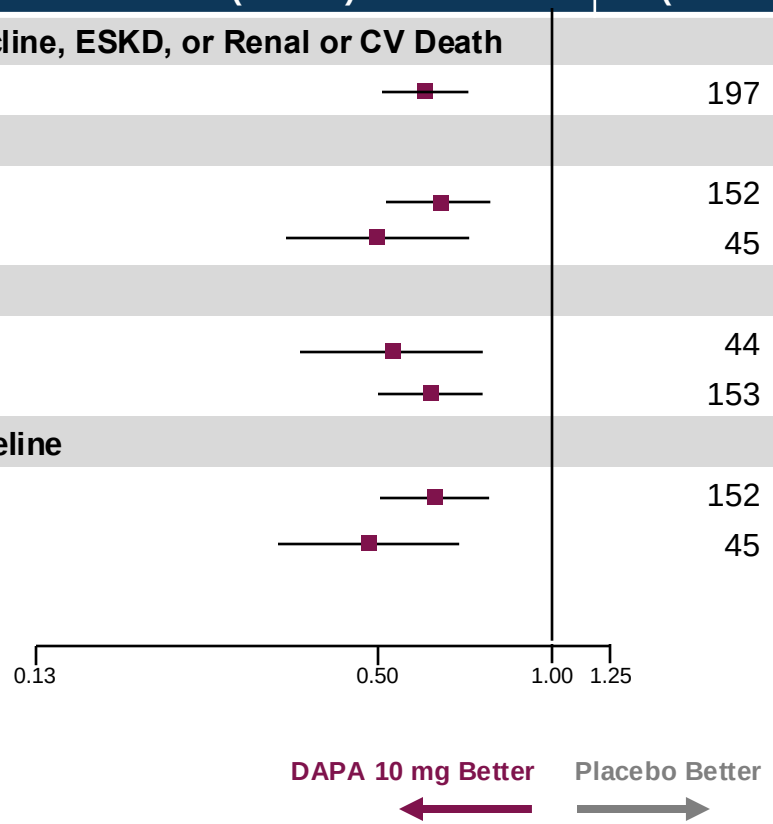
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020;

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

Primary Composite Outcome: Treatment Benefit Consistent Across Prespecified Subgroups[1]

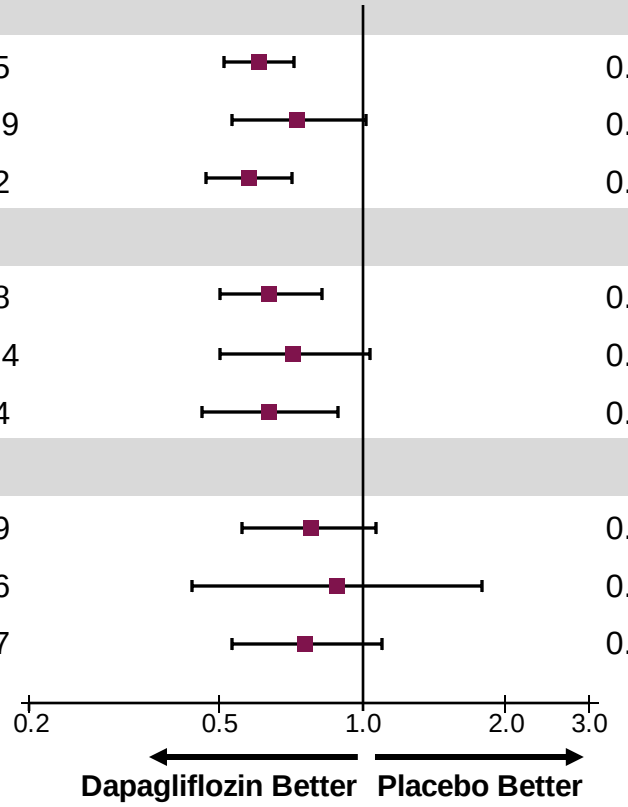
	Number of Events				
	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value Interaction[2]
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline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



1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

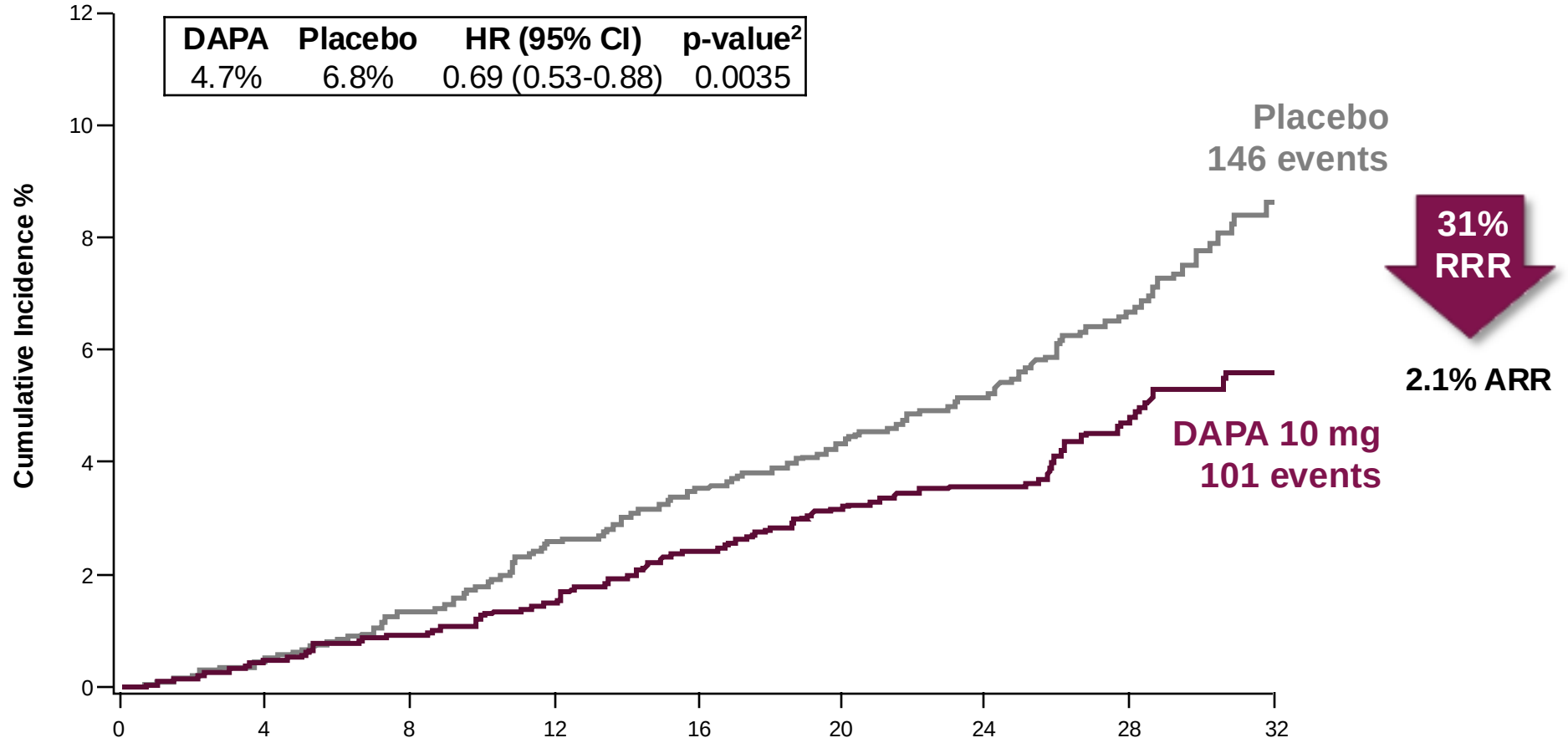
Primary Outcome According to CKD Stage

	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
	No. of patients/total no.		Events/100 patient-years			
Primary outcome: ≥50% eGFR decline, ESKD, kidney or CV death						
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
Stage 4	59/293	87/331	11.1	14.9	0.73 (0.53, 1.02)	0.22
Stage 2/3	138/1859	225/1821	3.7	6.2	0.58 (0.47, 0.71)	
ESKD						
Overall	109/2152	161/2152	2.5	3.8	0.64 (0.50, 0.82)	
Stage 4	49/293	72/331	9.2	12.4	0.72 (0.50, 1.04)	0.64
Stage 2/3	60/1859	89/1821	1.6	2.4	0.64 (0.46, 0.89)	
Kidney or CV death						
Overall	67/2152	86/2152	1.4	1.9	0.78 (0.56, 1.07)	
Stage 4	14/293	18/331	2.3	2.6	0.89 (0.44, 1.79)	0.74
Stage 2/3	53/1859	68/1821	1.3	1.7	0.76 (0.53, 1.09)	



Chertow GM et al. *J Am Soc Nephrol*. 2021;32:2352-2361.

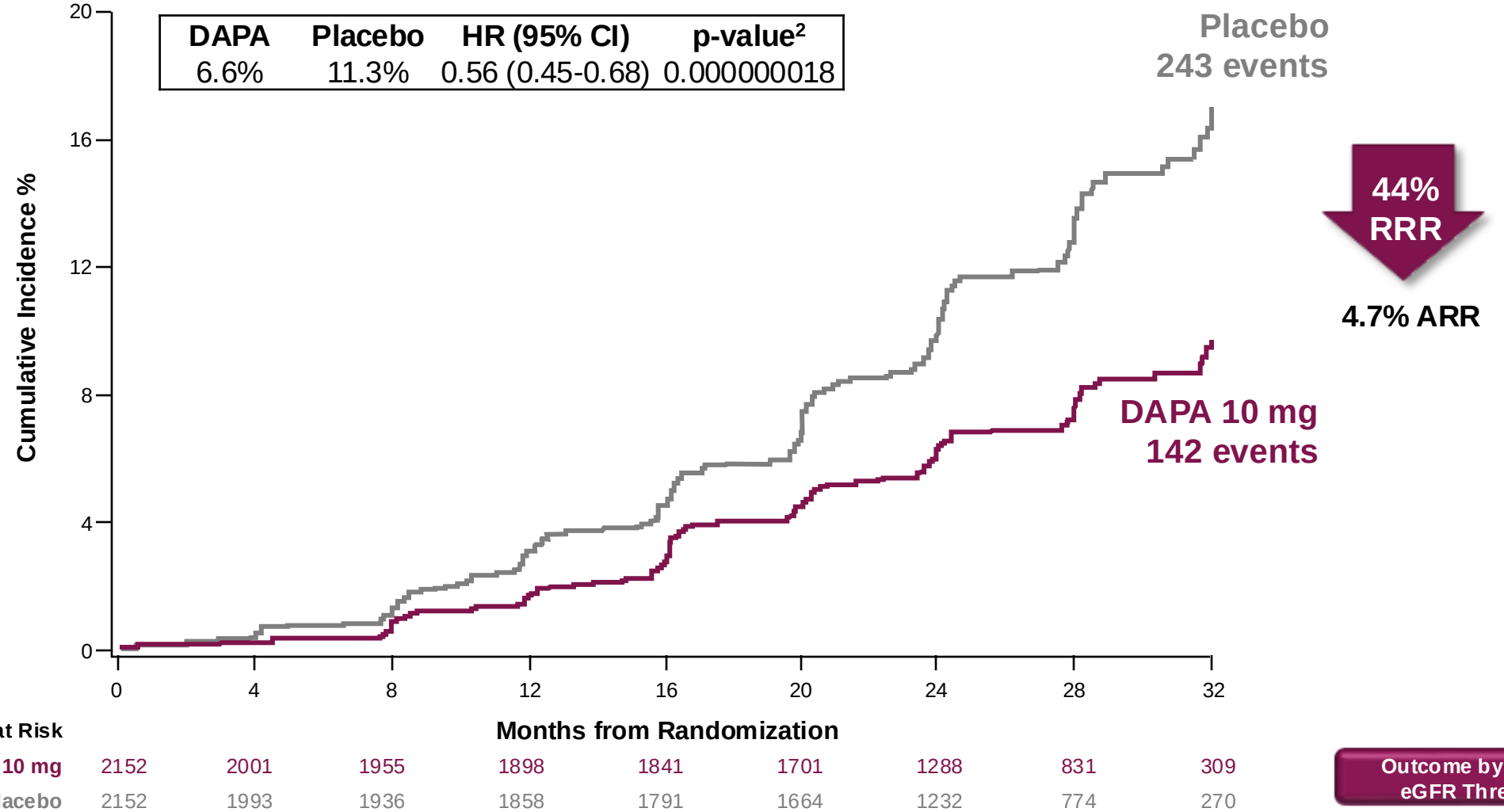
Secondary Outcome: All-cause Mortality[1]



ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

Secondary Renal-Specific Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a,1]



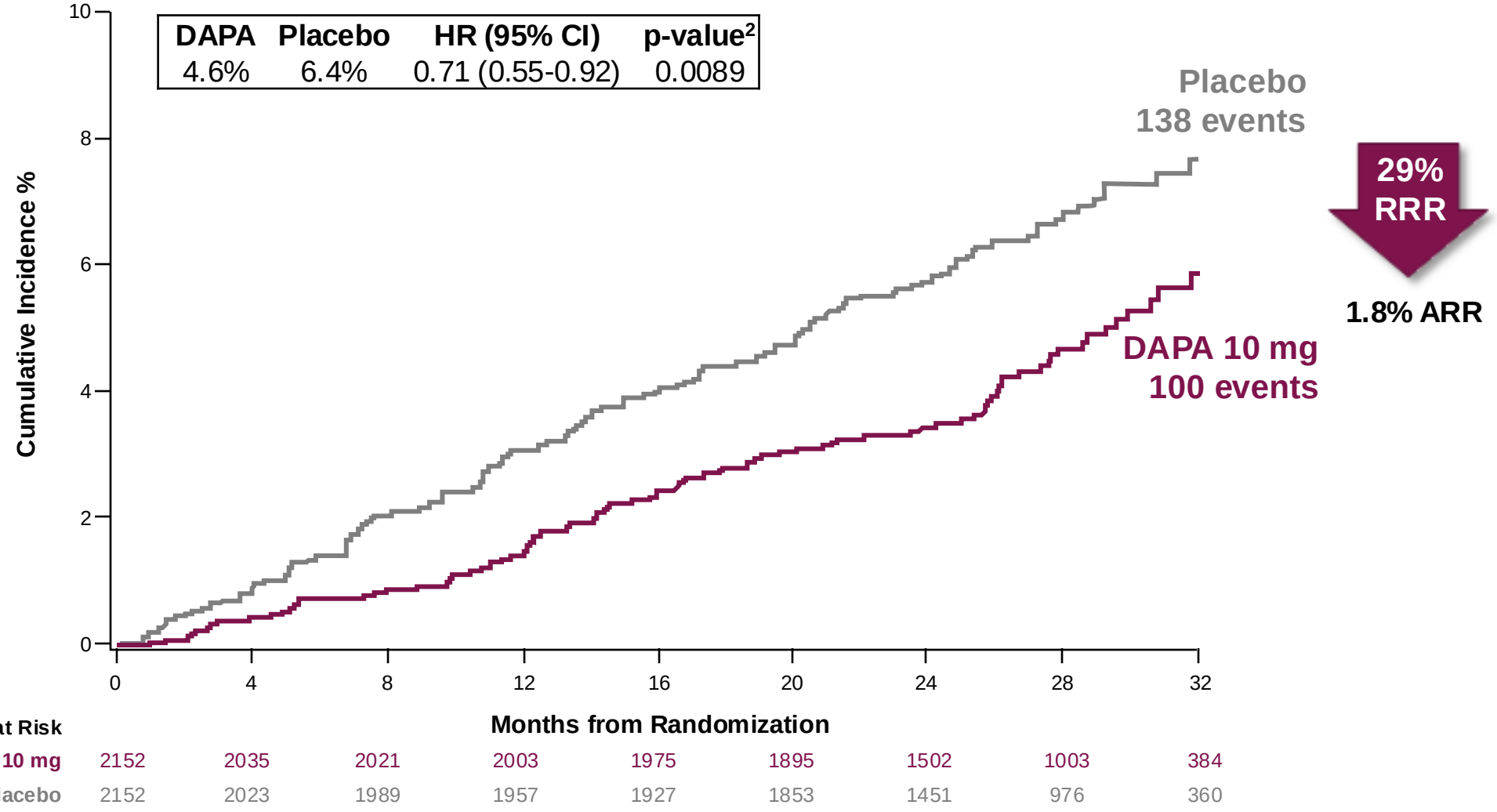
Outcome by Different eGFR Thresholds

[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

ARR = absolute risk reduction; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

Secondary Composite Outcome: CV Death or Hospitalization for Heart Failure[1]

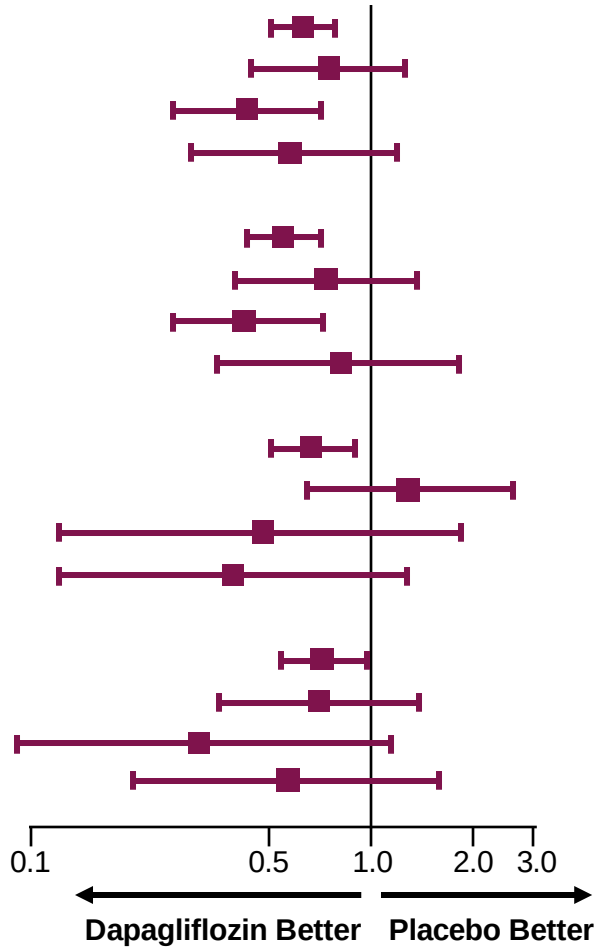


ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

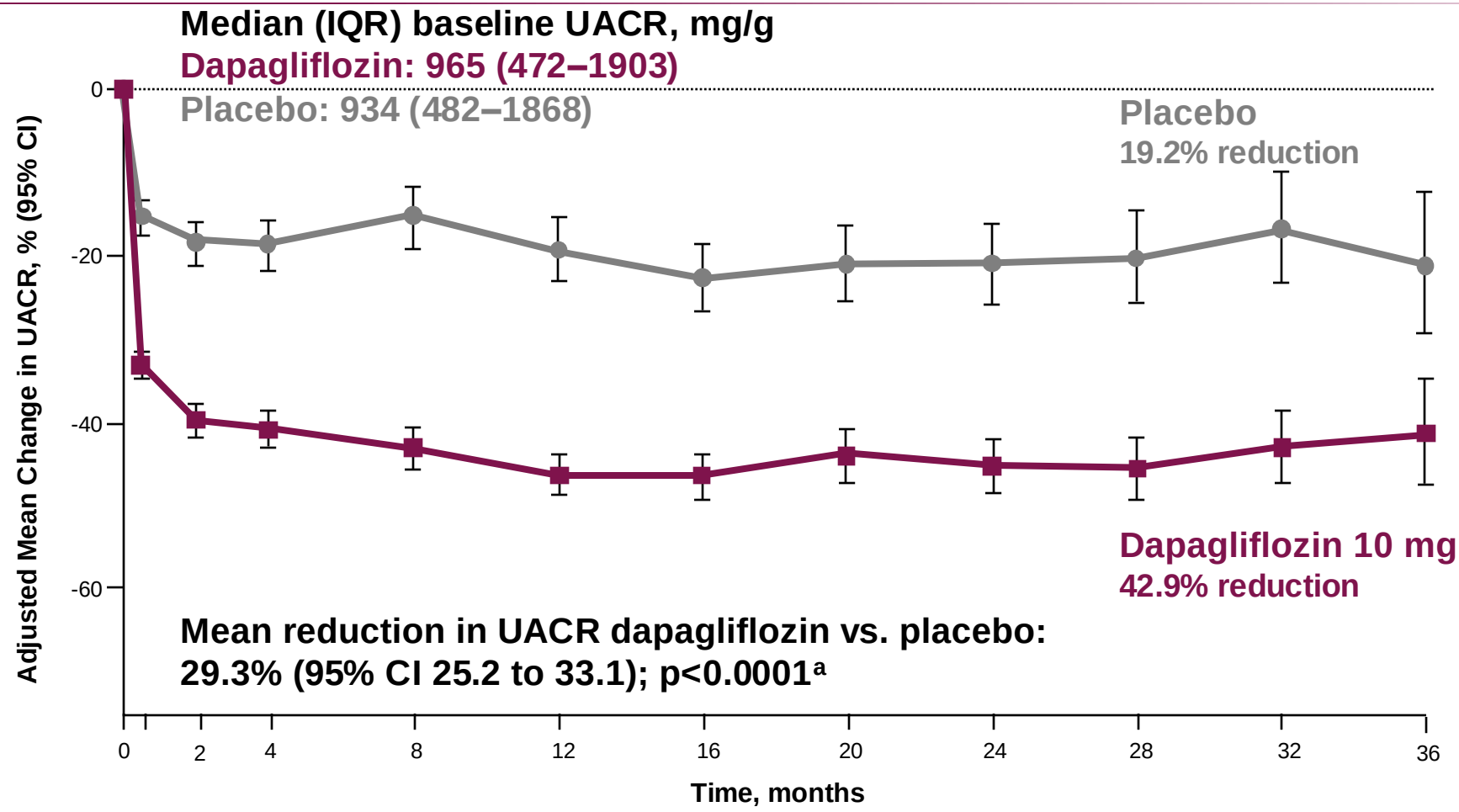
Primary and Secondary Outcomes by Underlying Cause of Kidney Disease

	Dapagliflozin 10 mg Events[a]	Placebo Events[a]	Hazard Ratio (95% CI)	P-value for Interaction
Primary outcome[b]				
Diabetic nephropathy	139/1271	207/1239	0.63 (0.51, 0.78)	0.53
Ischemic/hypertensive CKD	24/324	35/363	0.75 (0.44, 1.26)	
Glomerulonephritis	22/343	49/352	0.43 (0.26, 0.71)	
Other/unknown	12/214	21/198	0.58 (0.29, 1.19)	
Renal-specific outcomes[c]				
Diabetic nephropathy	93/1271	157/1239	0.55 (0.43, 0.71)	0.67
Ischemic/hypertensive CKD	18/324	26/363	0.74 (0.40, 1.36)	
Glomerulonephritis	21/343	46/352	0.43 (0.26, 0.72)	
Other/unknown	10/214	14/198	0.81 (0.35, 1.83)	
CV death or hHF				
Diabetic nephropathy	76/1271	107/1239	0.67 (0.50, 0.90)	0.24
Ischemic/hypertensive CKD	17/324	15/363	1.29 (0.64, 2.60)	
Glomerulonephritis	3/343	7/352	0.48 (0.12, 1.84)	
Other/unknown	4/214	9/198	0.39 (0.12, 1.28)	
All-cause mortality				
Diabetic nephropathy	78/1271	104/1239	0.72 (0.54, 0.97)	0.55
Ischemic/hypertensive CKD	14/324	22/363	0.70 (0.36, 1.37)	
Glomerulonephritis	3/343	11/352	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	0.57 (0.20, 1.61)	



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

Change in Albuminuria in the Overall Population



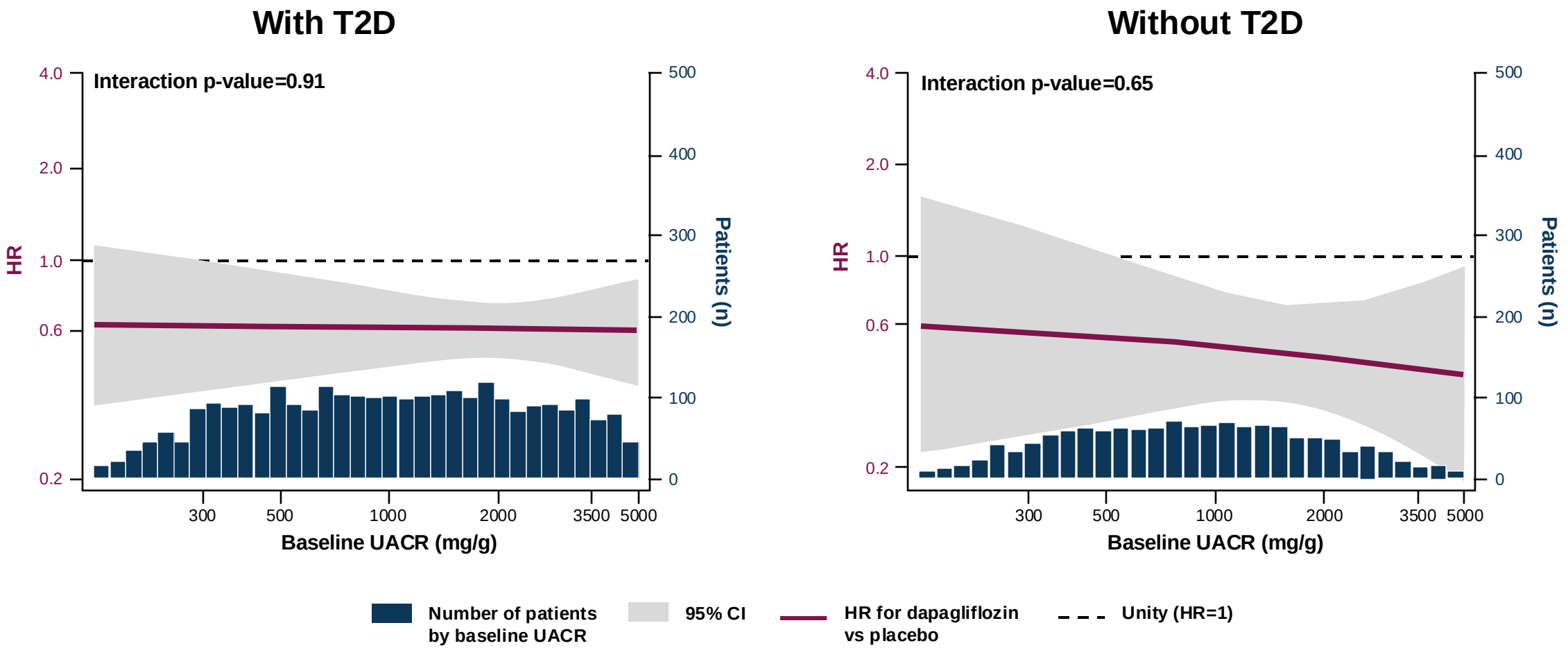
Dapagliflozin	2152	2085	2047	2048	1943	1884	1843	1778	1631	1172	692	233
Placebo	2152	2090	2054	2033	1909	1854	1818	1748	1581	1135	640	229

[a]Effect of dapagliflozin relative to placebo on UACR in the full cohort using the average coefficient of treatment to estimate the effect of dapagliflozin on the geometric mean UACR across the follow-up assessments.

CI = confidence interval; IQR = interquartile range; UACR = urinary albumin-to-creatinine ratio

Jongs N et al. *Lancet Diabetes Endocrinol*. 2021;9:755-766.

Post-hoc Analysis: Primary Composite Outcome[a] Across Baseline UACR Levels in Patients With and Without T2D



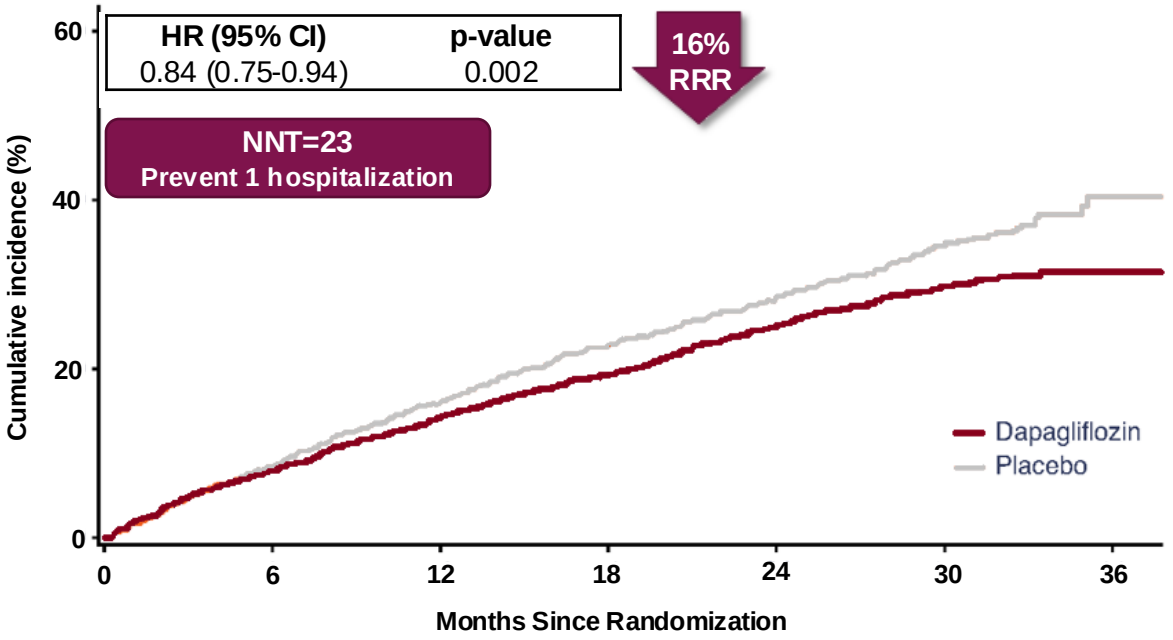
[a]Sustained ≥50% eGFR decline, ESKD, renal death, or CV death.

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

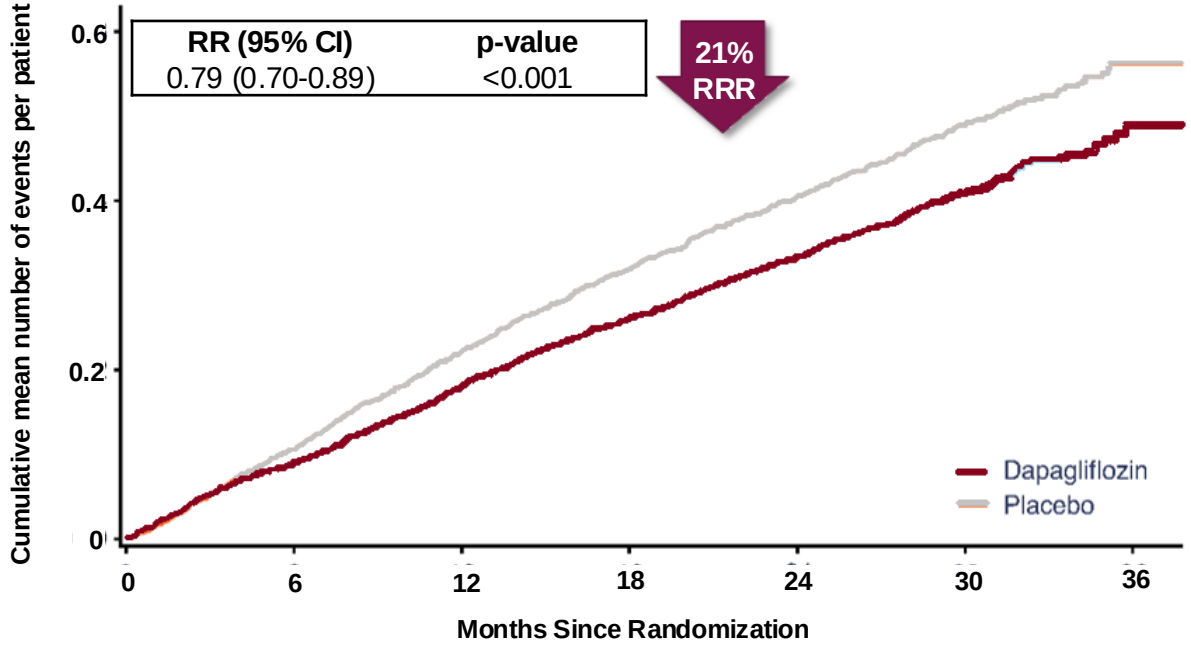
Waijer SW et al. *Diabetologia.* 2022;65(7):1085-1097.

Post-hoc Analysis: Dapagliflozin Reduced the Risk of All-cause Hospitalizations[1,2,a]

First Hospitalization



All Hospitalizations[b] or Death



- All hospitalizations[b,c] were observed to be lower with dapagliflozin than placebo (RRR, 22%; RR, 0.78; 95% CI, 0.70-0.87)
- There was a lower rate of hospital admissions related to cardiac, renal and urinary, metabolism and nutrition, and neoplastic disorders observed with dapagliflozin

[a]Post hoc analysis; [b]First and subsequent; [c]Assessed in a sensitivity analysis using a joint frailty model.

HR = hazard ratio; NNT = number needed to treat; RR = rate ratio; RRR = relative risk reduction.

1. Schechter M et al *Ann Intern Med.* 2023;176(1):59-66; 2. Schechter M et al. Presented at: ASN Kidney Week; November 3-6, 2022; Orlando, FL.

Safety Outcomes[1]

Safety Outcomes[a], n (%)	Dapagliflozin 10 mg (n=2149)	Placebo (n=2149)	p-value
Discontinuation of study drug	274 (12.7)	309 (14.4)	NA
Discontinuation due to adverse event	118 (5.5)	123 (5.7)	0.79
Any serious adverse event	633 (29.5)	729 (33.9)	0.002
Adverse events of interest			
Amputation[b]	35 (1.6)	39 (1.8)	0.73
Any definite or probable diabetic ketoacidosis	0	2 (0.1)	0.50
Fracture[c]	85 (4.0)	69 (3.2)	0.22
Renal-related adverse event[c]	155 (7.2)	188 (8.7)	0.07
Major hypoglycemia[d]	14 (0.7)	28 (1.3)	0.04
Volume depletion[c]	127 (5.9)	90 (4.2)	0.01
Serious adverse events of volume depletion[2]	22 (1.0)	18 (0.8)	NA
Fournier's Gangrene	0	1(<0.1)	NA

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

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Discontinuations and Serious AEs of UTIs and Genital Infections by Diabetes Status[a]

	With T2D		Without T2D	
	Dapagliflozin 10 mg(n=1453)	Placebo (n=1450)	Dapagliflozin 10 mg (n=696)	Placebo (n=699)
Discontinuation due to any AE of UTI, n (%)	7 (0.5)	3 (0.2)	1 (0.1)	0
UTI	6 (0.4)	3 (0.2)	1 (0.1)	0
Urogenital infection bacterial	1 (0.1)	0	0	0
Discontinuation due to any AE of genital infection, n(%)	3 (0.2)	0	0	0
Vulvovaginal mycotic infection	2 (0.1)	0	0	0
Urogenital infection bacterial	1 (0.1)	0	0	0
Any SAE of UTI, n (%)	23 (1.6)	14 (1.0)	6 (0.9)	4 (0.6)
UTI	17 (1.2)	10 (0.7)	3 (0.4)	3 (0.4)
Pyelonephritis acute	2 (0.1)	1 (0.1)	3 (0.4)	0
Cystitis	1 (0.1)	2 (0.1)	0	0
Escherichia urinary tract infection	1 (0.1)	0	0	0
Pyonephrosis	1 (0.1)	0	0	0
UTI bacterial	1 (0.1)	0	0	0
Urogenital infection bacterial	1 (0.1)	0	0	0
Pyelonephritis	0	1 (0.1)	1 (0.1)	1 (0.1)
Any SAE of genital infection, n (%)	3 (0.2)	0	0	0
Balanoposthitis	1 (0.1)	0	0	0
Urogenital infection bacterial	1 (0.1)	0	0	0
Vulval cellulitis	1 (0.1)	0	0	0

aSafety analysis set.

AE = adverse event; SAE = serious adverse event; T2D = type 2 diabetes; UTI = urinary tract infection.

Wheeler DC et al. Article and supplementary appendix. Lancet Diabetes Endocrinol. 2021;9:22–31.

SGLT2 Inhibitor Use in Chronic Kidney Disease: Supporting Cardiovascular, Kidney, and Metabolic Health

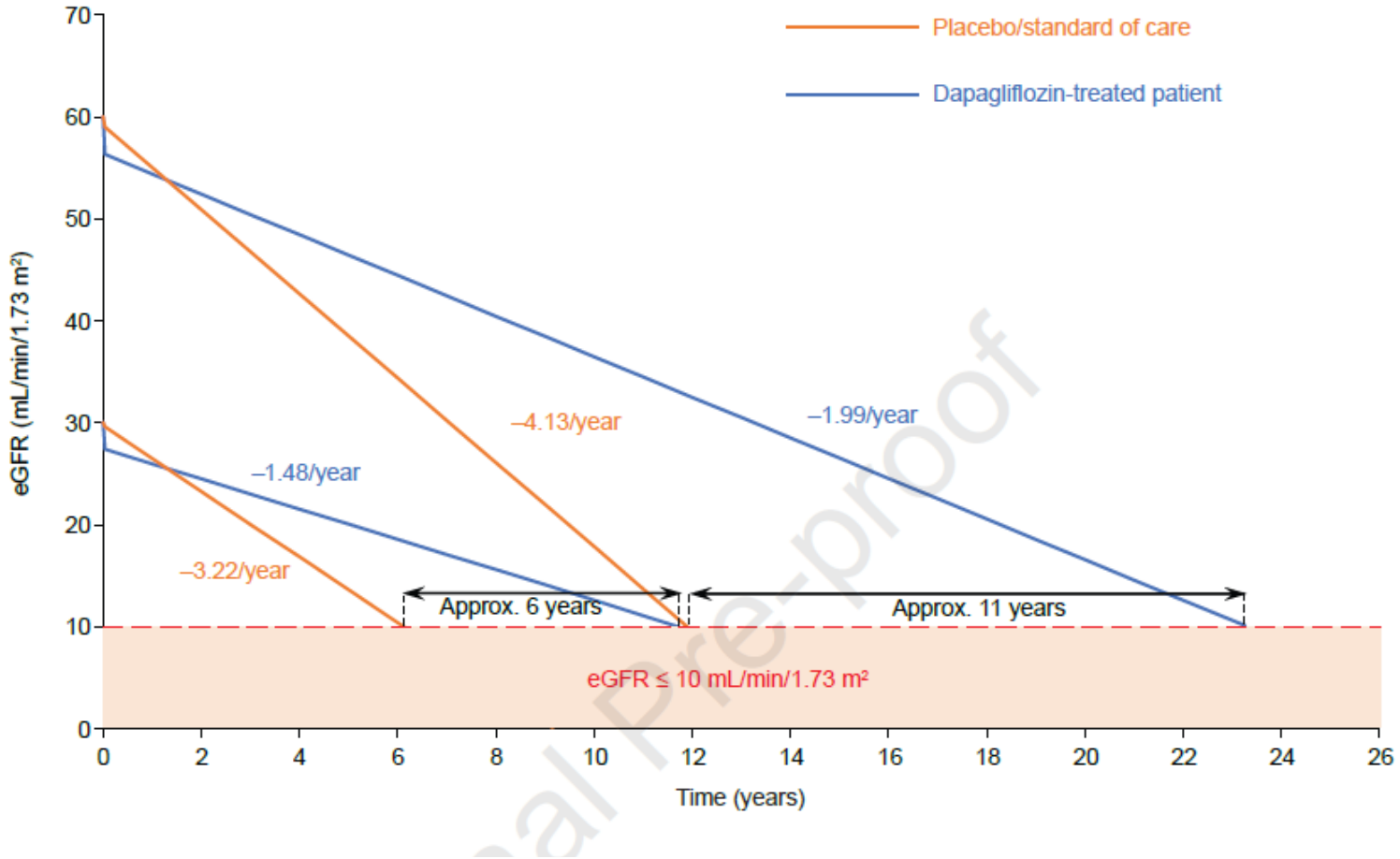
Magdalena Madero, MD, Glenn M. Chertow, MD, MPH, Patrick B. Mark, MB, ChB, PhD

Kidney Medicine
An Official Journal of the National Kidney Foundation

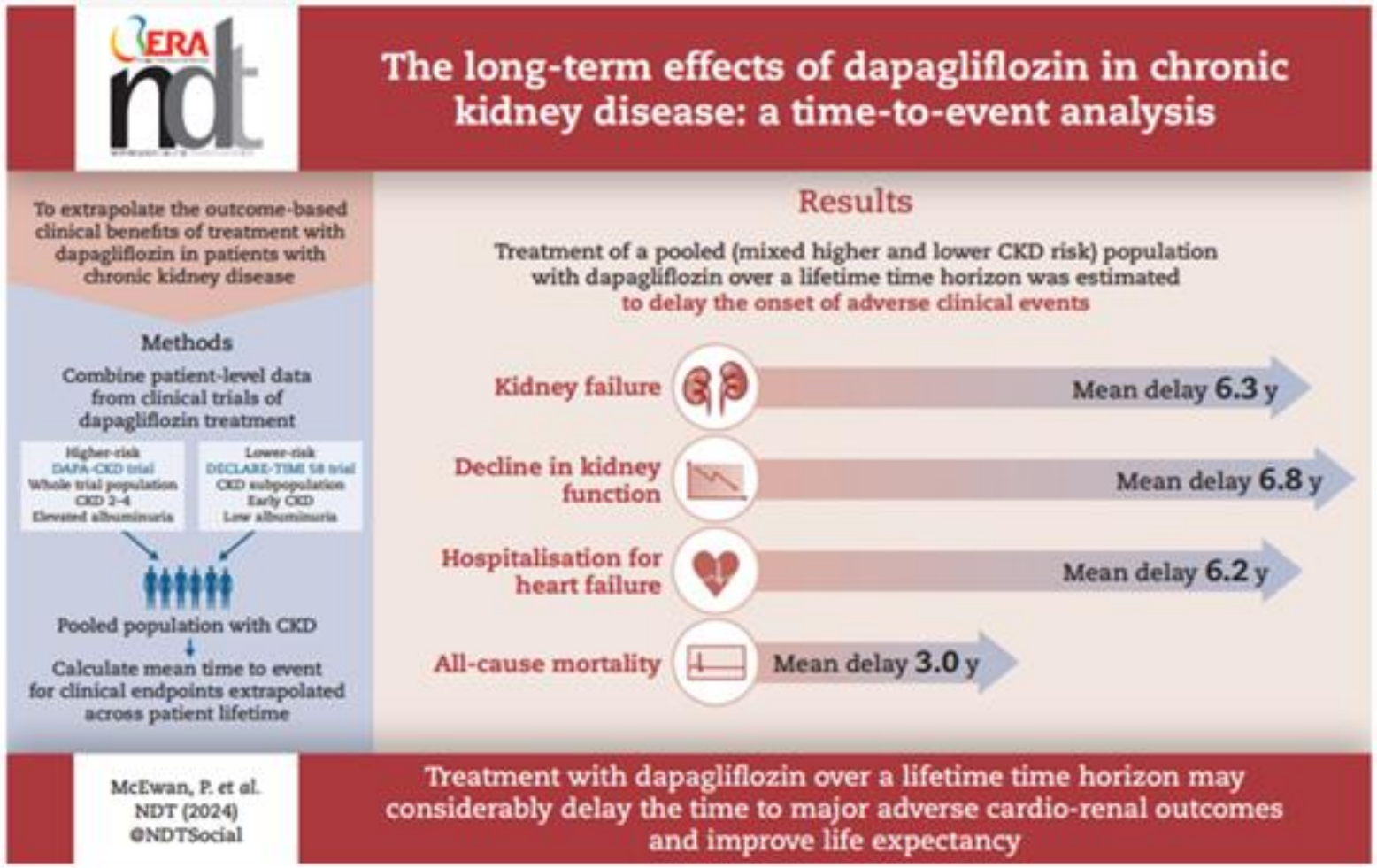
initiation

1. When should a patient taking a RAS inhibitor for the treatment of CKD initiate an SGLT2 inhibitor?
   - ✓ alongside a RAS inhibitor
   - ✓ monotherapy

3. Should patients at lower risk of progression still initiate SGLT2 inhibitor therapy?



The long-term effects of dapagliflozin in chronic kidney disease: a time-to-event analysis



McEwan P. et al. Nephrology Dialysis Transplantation, 2024

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