DAPA-CKD: Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease Trial

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Dapagliflozin: DAPA-CKD Trial

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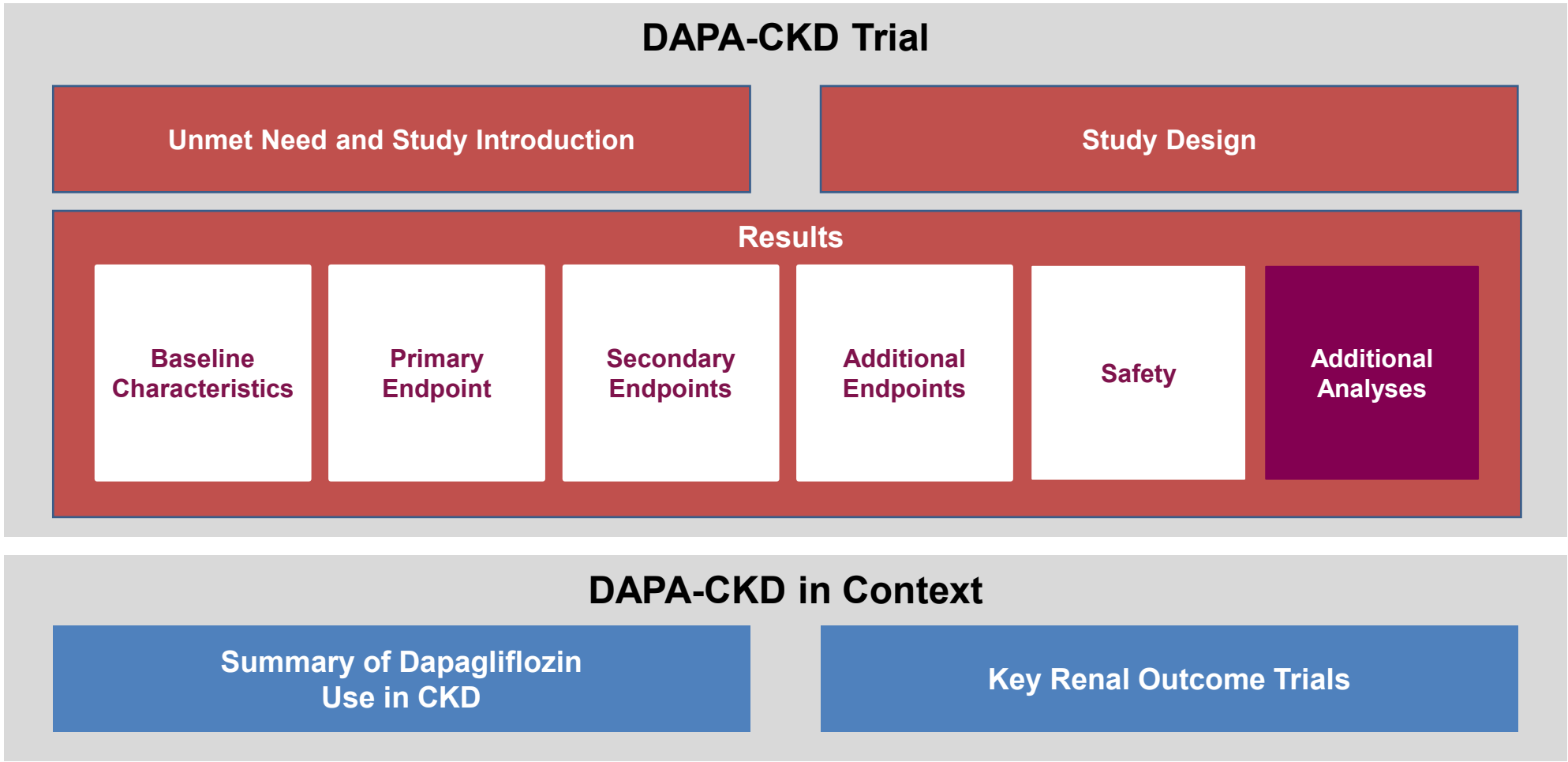


CKD = chronic kidney disease; CVD = cardiovascular disease; T2D = type 2 diabetes.

Rationale for DAPA-CKD

- CKD represents a global healthcare burden and is a significant contributor to CV morbidity, all-cause mortality and diminished quality of life[1]
- Until recently, the only classes of medication specifically proven to slow progression of CKD were ACEis or ARBs[2-5]
- The **DECLARE** trial demonstrated the beneficial effects of dapagliflozin on HF and potential benefits on renal outcomes* in patients with T2D with predominantly preserved renal function with or without established CV disease.[6]
- The **DAPA-HF** trial demonstrated that dapagliflozin reduced the risk of worsening HF or death from CV causes, and a potential to improve renal outcomes**, in patients with HFrEF, with or without T2D[7]
- The **DAPA-CKD** trial was designed to evaluate the effect of dapagliflozin on renal and CV outcomes and mortality in people with CKD, with or without T2D[8]

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; SGLT-2 = sodium glucose co-transporter 2; T2D = type 2 diabetes.

* Exploratory finding in DECLARE ** Non-significant renal result in DAPA-HF

1. GBD Chronic Kidney Disease Collaboration. *Lancet.* 2020;395:709-733. 2. Ruggenenti P et al. *Lancet.* 1999;354:359-364. 3. Hou FF et al. *N Engl J Med.* 2006;354:131-140. 4. Brenner BM et al. *N Engl J Med.* 2001;345:861-869. 5. Lewis EJ et al. *N Engl J Med.* 2001;345:851-860. 6. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357. 7. McMurray JJV et al. *N Engl J Med.* 2019; 381:1995-2008. 8. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Study Design

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 maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥22.6 to ≤565.6 mg/mmol (≥200 mg/g but ≤5000 mg/g)
- Stable max tolerated 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. Online ahead of print. *N Engl J Med*. 2020.

Countries Participating in DAPA-CKD[1,2]

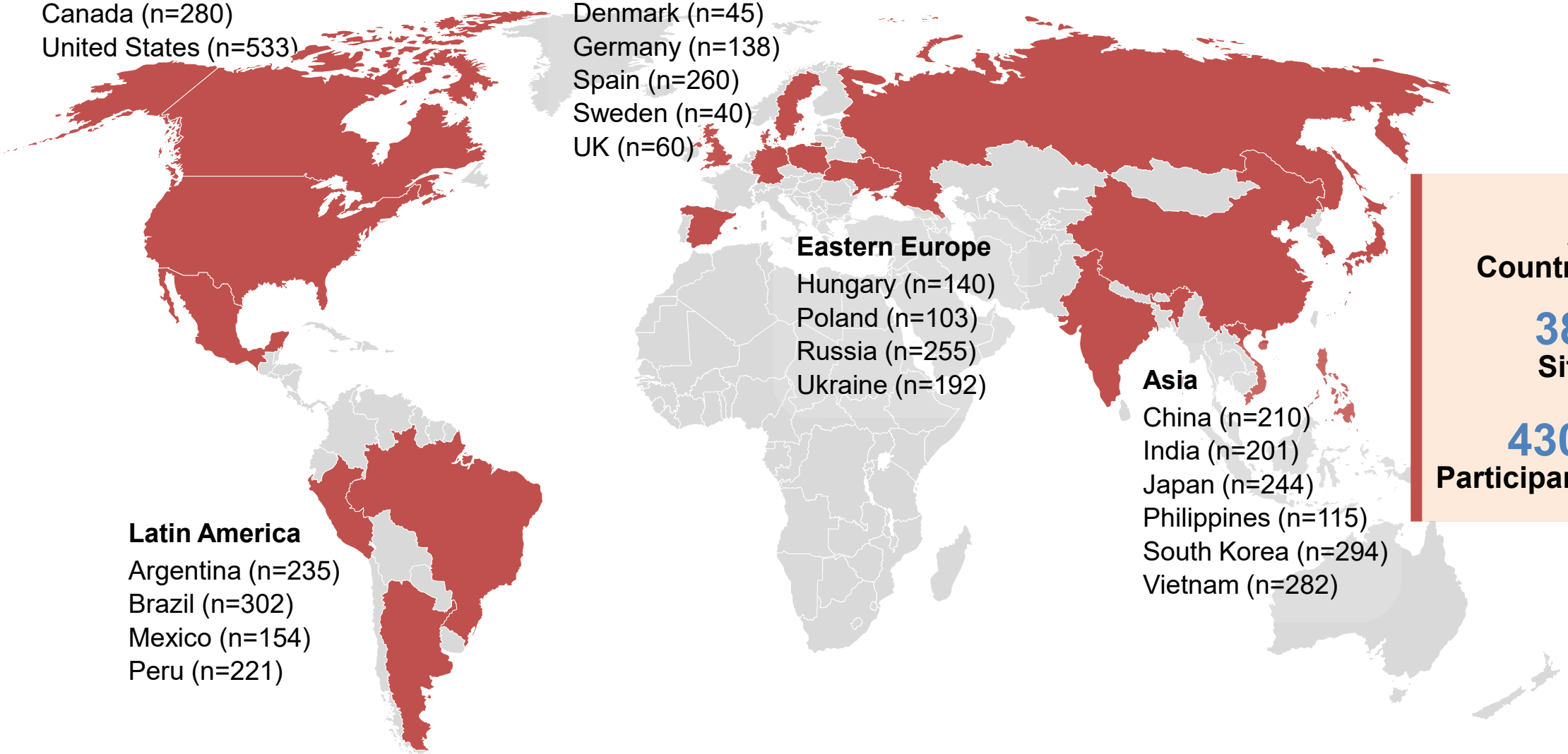
North America
Canada (n=280)
United States (n=533)

Western Europe
Denmark (n=45)
Germany (n=138)
Spain (n=260)
Sweden (n=40)
UK (n=60)

Eastern Europe
Hungary (n=140)
Poland (n=103)
Russia (n=255)
Ukraine (n=192)

Asia
China (n=210)
India (n=201)
Japan (n=244)
Philippines (n=115)
South Korea (n=294)
Vietnam (n=282)

Latin America
Argentina (n=235)
Brazil (n=302)
Mexico (n=154)
Peru (n=221)



21 Countries

386 Sites

4304 Participants

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.

Baseline Characteristics

Demographics and Baseline Characteristics

	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)
Age, years, mean	61.8	61.9
Gender, female, %	32.9	33.3
Race[a], %		
White	52.2	54.2
Black or African-American	4.8	4.0
Asian	34.8	33.4
Other	8.1	8.4
Weight, kg	81.5	82.0
Body mass index, kg/m^2	29.4	29.6
Current smoker, %	13.2	14.0
Blood pressure, mmHg, mean		
Systolic blood pressure	136.7	137.4
Diastolic blood pressure	77.5	77.5
Hemoglobin, g/L	128.6	127.9
Serum potassium, mEq/L	4.6	4.6

[a]Race was reported by the investigators; the designation 'other' includes Native Hawaiian or other Pacific Islander; American Indian or Alaska Native and Other.
BL = baseline.
Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446.

BL Characteristics by Diabetes Status

Renal Characteristics

	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)
eGFR, mL/min/1.73m^2, mean	43.2	43.0
eGFR ≥60 mL/min/1.73m^2, %	10.9	10.2
eGFR 45 to <60 mL/min/1.73m^2, %	30.0	31.7
eGFR 30 to <45 mL/min/1.73m^2, %	45.5	42.7
eGFR <30 mL/min/1.73m^2, %	13.6	15.4
UACR, mg/mmol, median UACR, mg/g, median	109 965	106 934
UACR >113 mg/mmol, % (UACR >1000 mg/g)	48.7	47.9

Renal Characteristics by Diabetes Status

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL et al. Online ahead of print. *N Engl J Med*. 2020.

Medical History and Baseline Medications

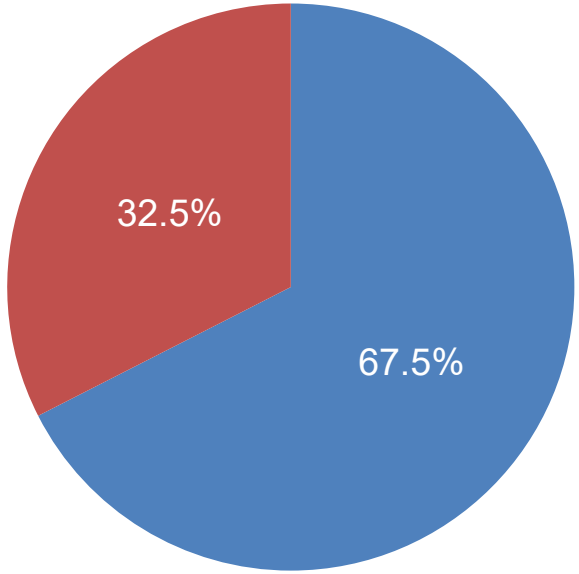
	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)
Type 2 diabetes, %	67.6	67.4
CV disease, %	37.8	37.0
Heart failure, %	10.9	10.8
Prior medication, %		
ACEi	31.3	31.6
ARB	67.1	66.3
Diuretic	43.1	44.3
Statin	64.8	65.0

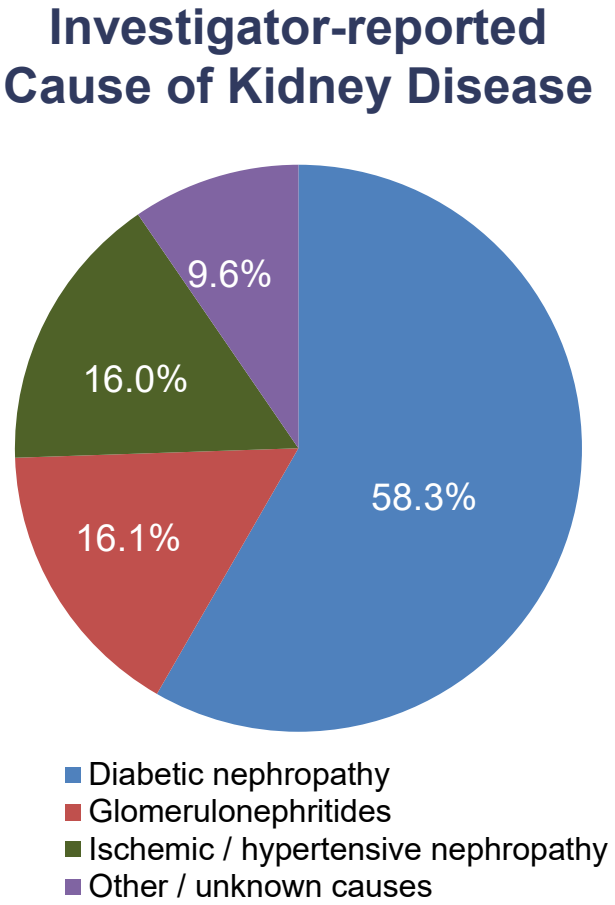
BL Characteristics by Diabetes Status

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BL = baseline; CKD = chronic kidney disease; CV = cardiovascular

Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446.

Diabetes Status and Investigator-reported Cause of Kidney Disease at Baseline



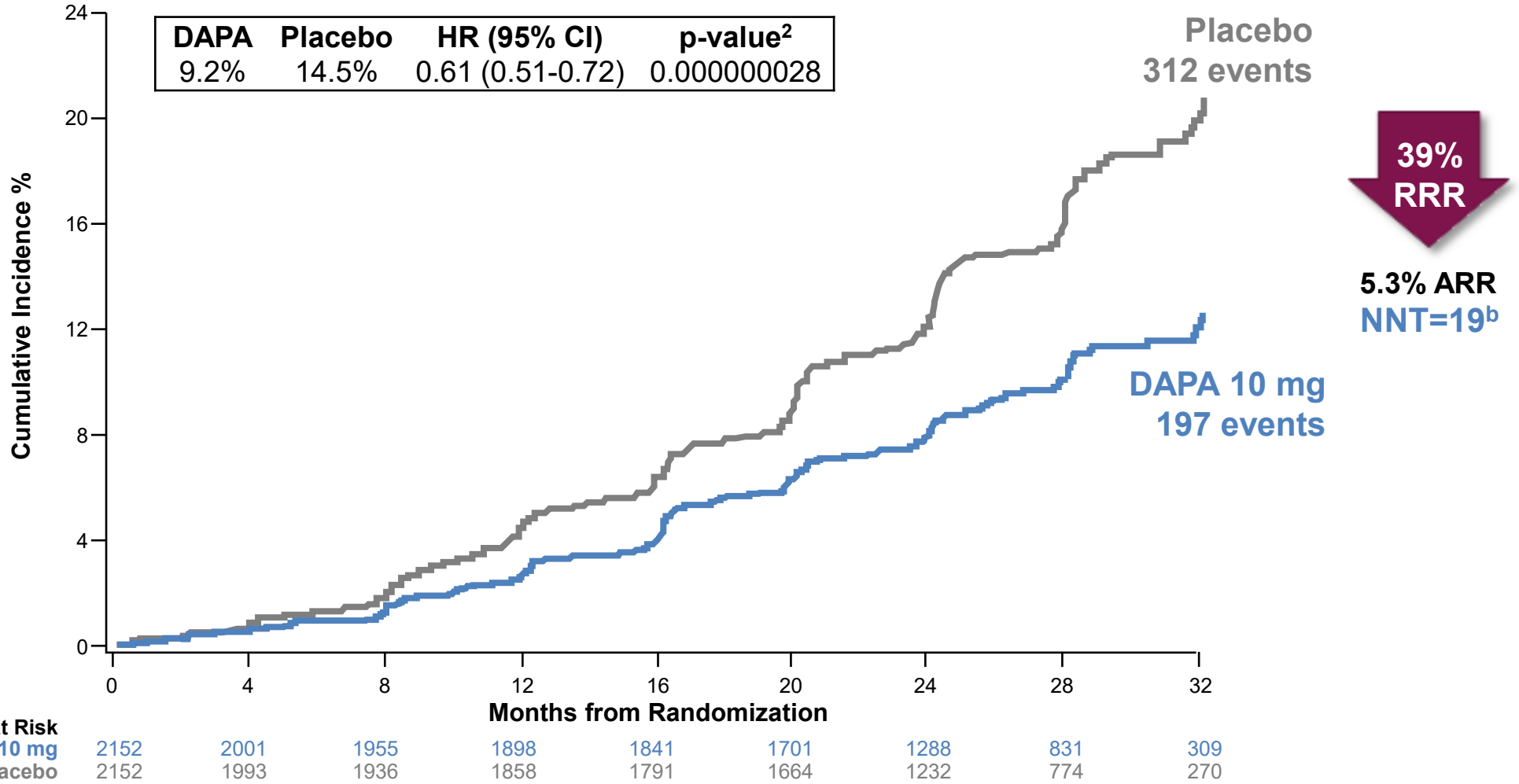


CKD Etiologies

Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Efficacy Endpoints

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.

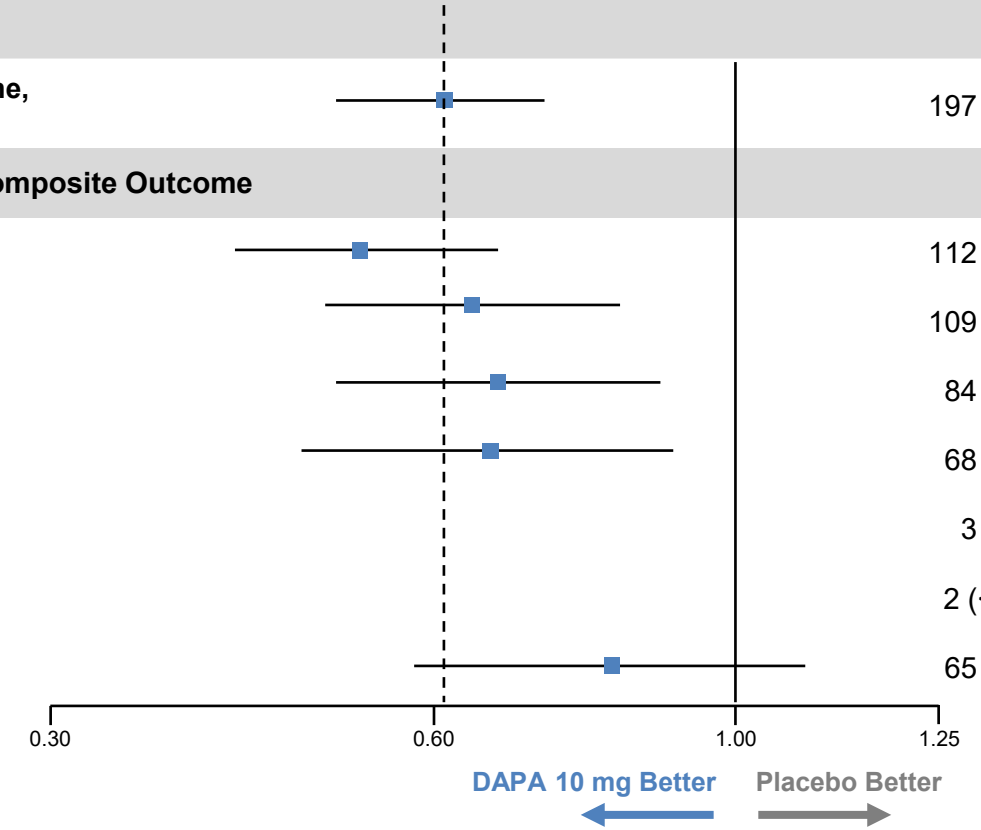
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

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.

Individual Components of the Primary Composite Outcome[1]

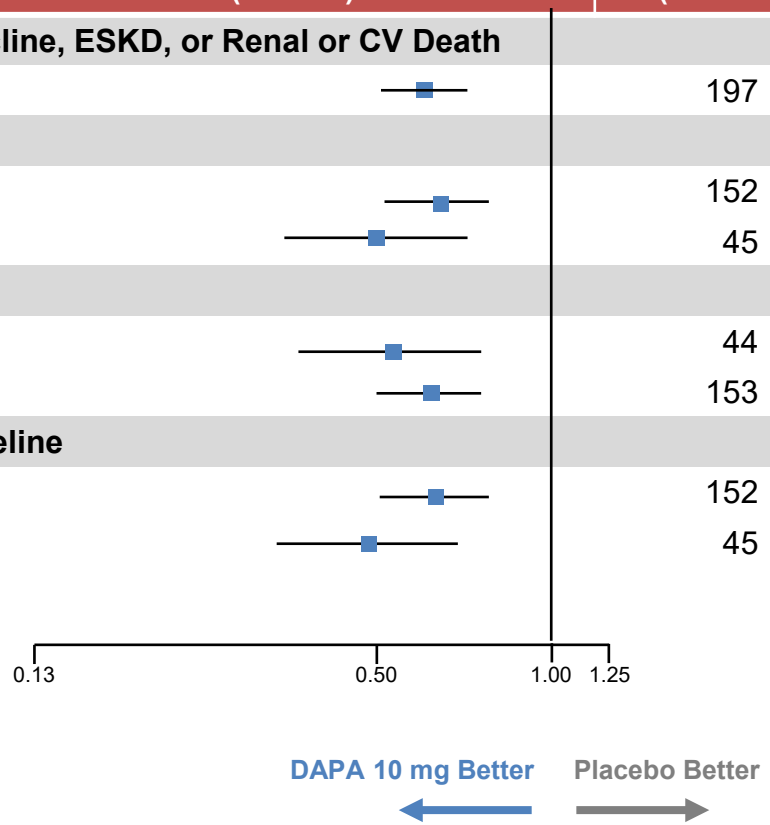
	Number of Events (%)				
	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value[2]
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome					
≥50% eGFR Decline	112 (5.2)	201 (9.3)	0.53	(0.42, 0.67)	<0.0001
ESKD	109 (5.1)	161 (7.5)	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m^2	84 (3.9)	120 (5.6)	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis[a]	68 (3.2)	99 (4.6)	0.66	(0.48, 0.90)	0.0080
Transplantation[a]	3 (0.1)	8 (0.4)	NC		
Renal Death	2 (<0.1)	6 (0.3)	NC		
CV Death	65 (3.0)	80 (3.7)	0.81	(0.58, 1.12)	0.2029



[a]There were 69 endpoint events for dapagliflozin and 100 endpoint events for placebo for the combined chronic dialysis and renal transplantation endpoint (HR 0.66; 95% CI 0.49, 0.90).
CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable
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 Composite Outcome: Prespecified Subgroup Analyses[1]

	Number of Events				
HR (95% CI)	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/1.73m²) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	

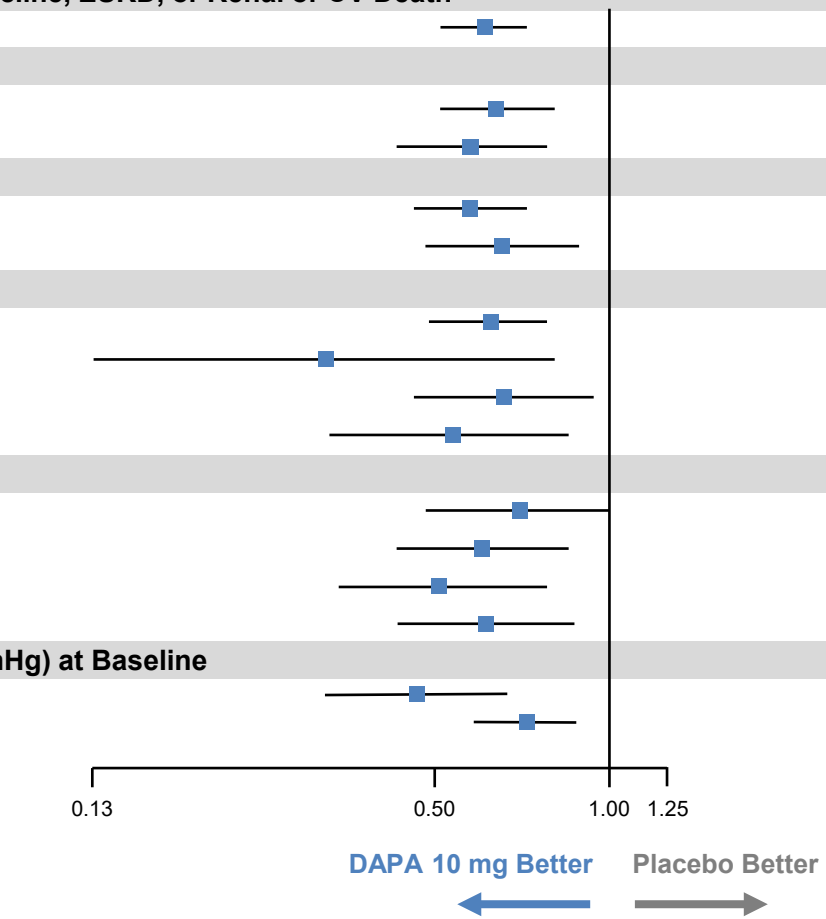


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

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 Composite Outcome: Prespecified Subgroup Analyses[1]

	Number of Events				
HR (95% CI)	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)	
Age (years)					0. 53
≤65	122	191	0.64	(0.51, 0.80)	
>65	75	121	0.58	(0.43, 0.77)	
Gender					0.50
Male	126	209	0.57	(0.46, 0.72)	
Female	71	103	0.65	(0.48, 0.88)	
Race					0.68
White	110	174	0.62	(0.49, 0.79)	
Black	7	14	0.33	(0.13, 0.81)	
Asian	53	77	0.66	(0.46, 0.93)	
Other	27	47	0.54	(0.33, 0.86)	
Geographic Region					0.77
Asia	50	69	0.70	(0.48, 1.00)	
Europe	57	89	0.60	(0.43, 0.85)	
North America	35	69	0.51	(0.34, 0.76)	
Latin America	55	85	0.61	(0.43, 0.86)	
Systolic Blood Pressure (mmHg) at Baseline					0.04
≤130	46	96	0.44	(0.31, 0.63)	
>130	151	216	0.68	(0.56, 0.84)	

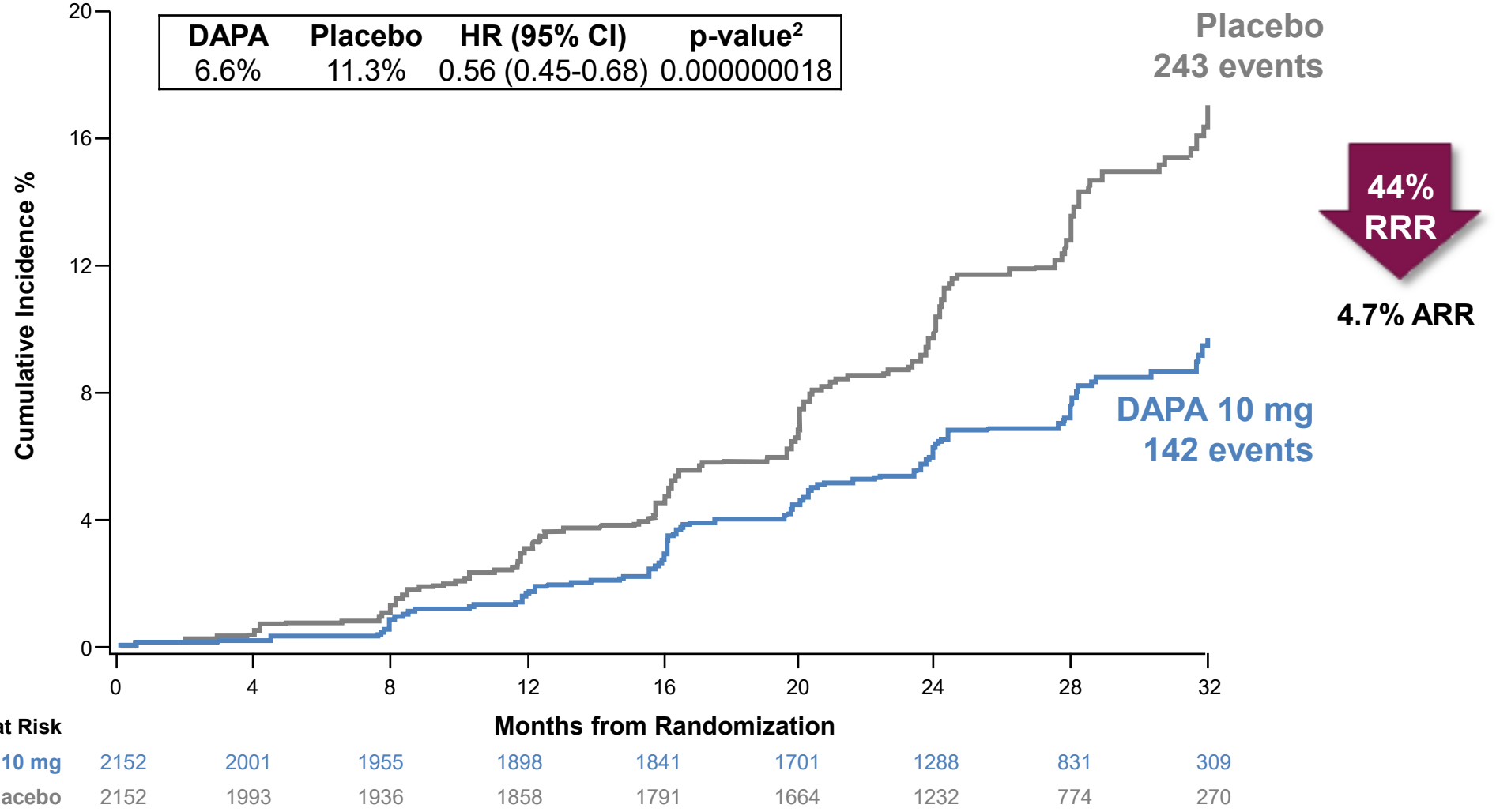


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio.

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 Endpoints

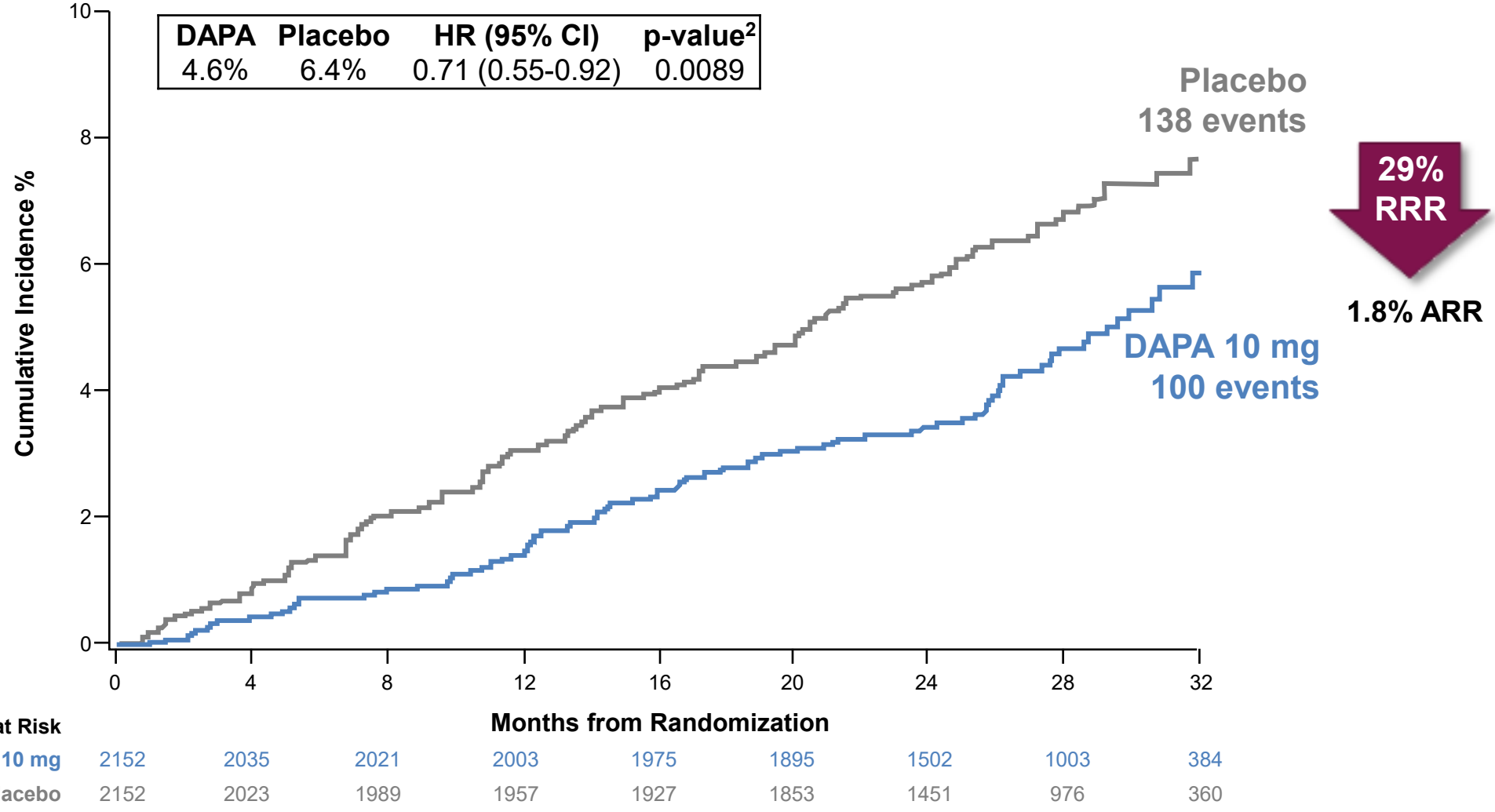
Secondary Renal-Specific Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a,1]



[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.[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.

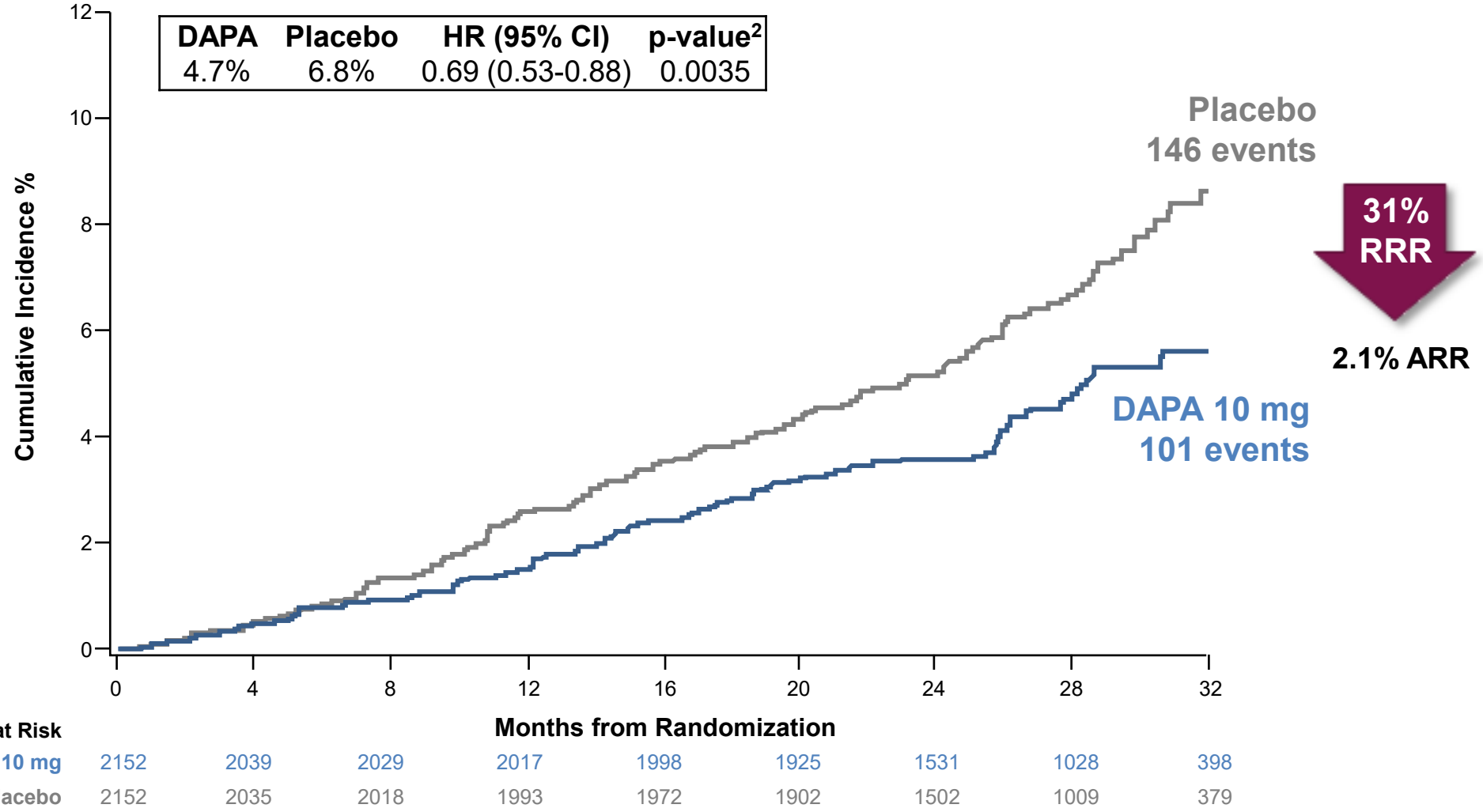
Secondary Composite Outcome: CV Death or Hospitalization for Heart Failure[1]



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.

Secondary Outcome: All-cause Mortality[1]

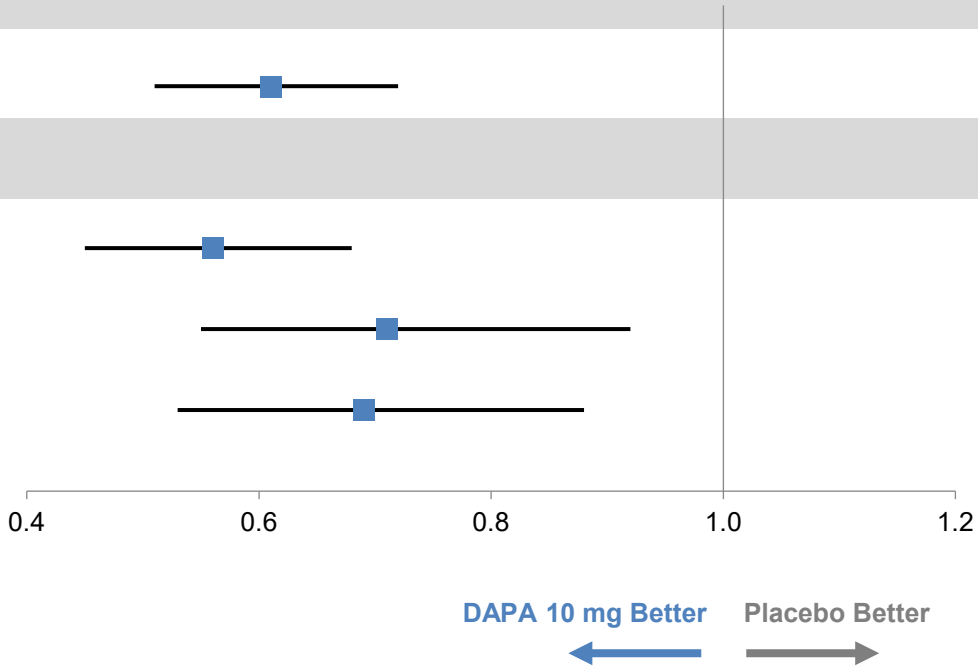


ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

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.

Statistical Significance Achieved for the Primary and All Secondary Outcomes[1]

	Number of Events (%)				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	Hazard Ratio	95% CI	p-value[2]
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, and Renal or CV Death	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	<0.0001
Secondary Outcomes					
Composite of ≥50% eGFR Decline, ESKD, or Renal Death	142 (6.6)	243 (11.3)	0.56	(0.45, 0.68)	<0.0001
Composite of CV Death or Hospitalization for HF	100 (4.6)	138 (6.4)	0.71	(0.55, 0.92)	0.0089
All-cause mortality	101 (4.7)	146 (6.8)	0.69	(0.53, 0.88)	0.0035

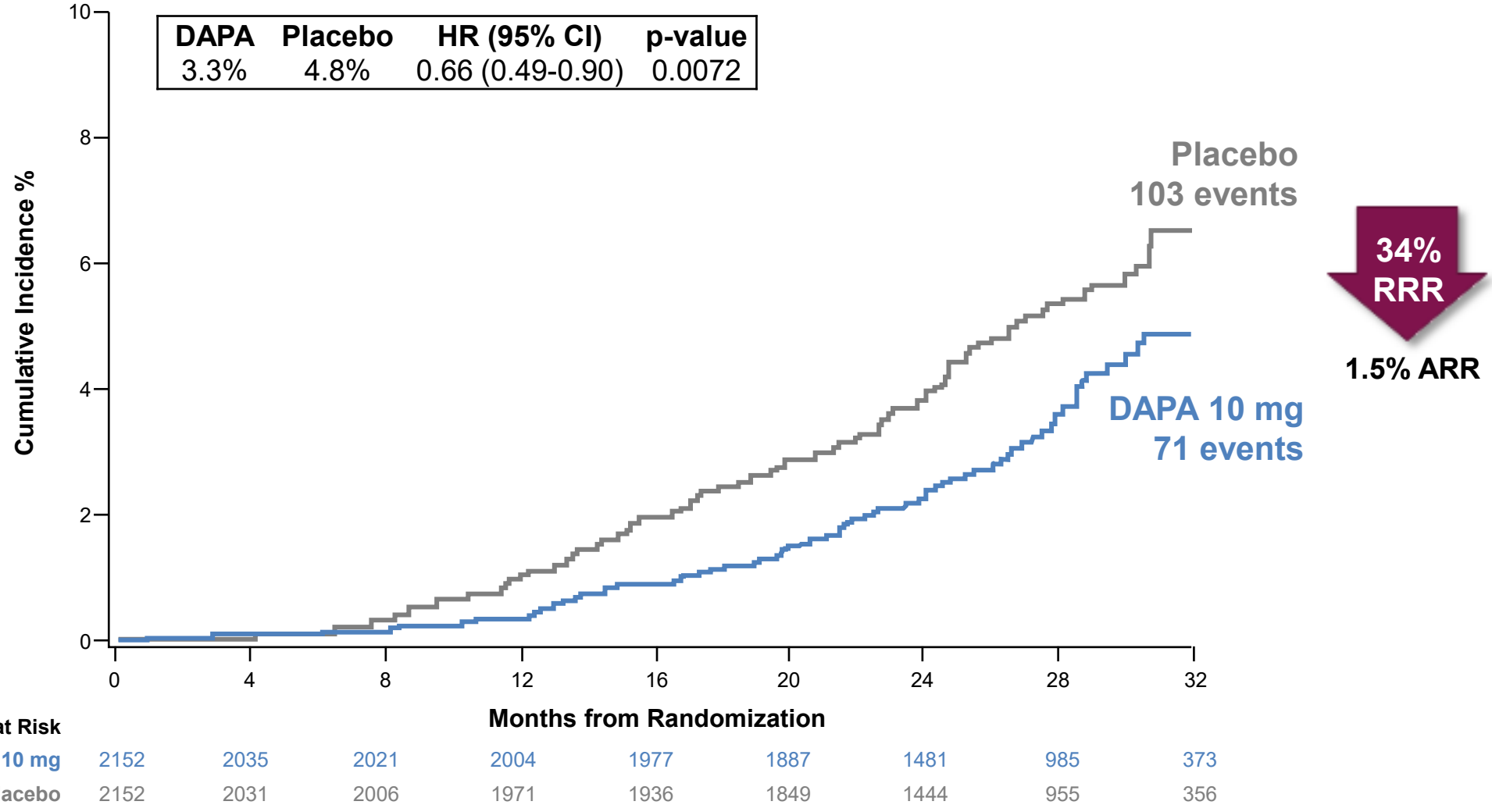


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure.

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.

Additional Endpoints

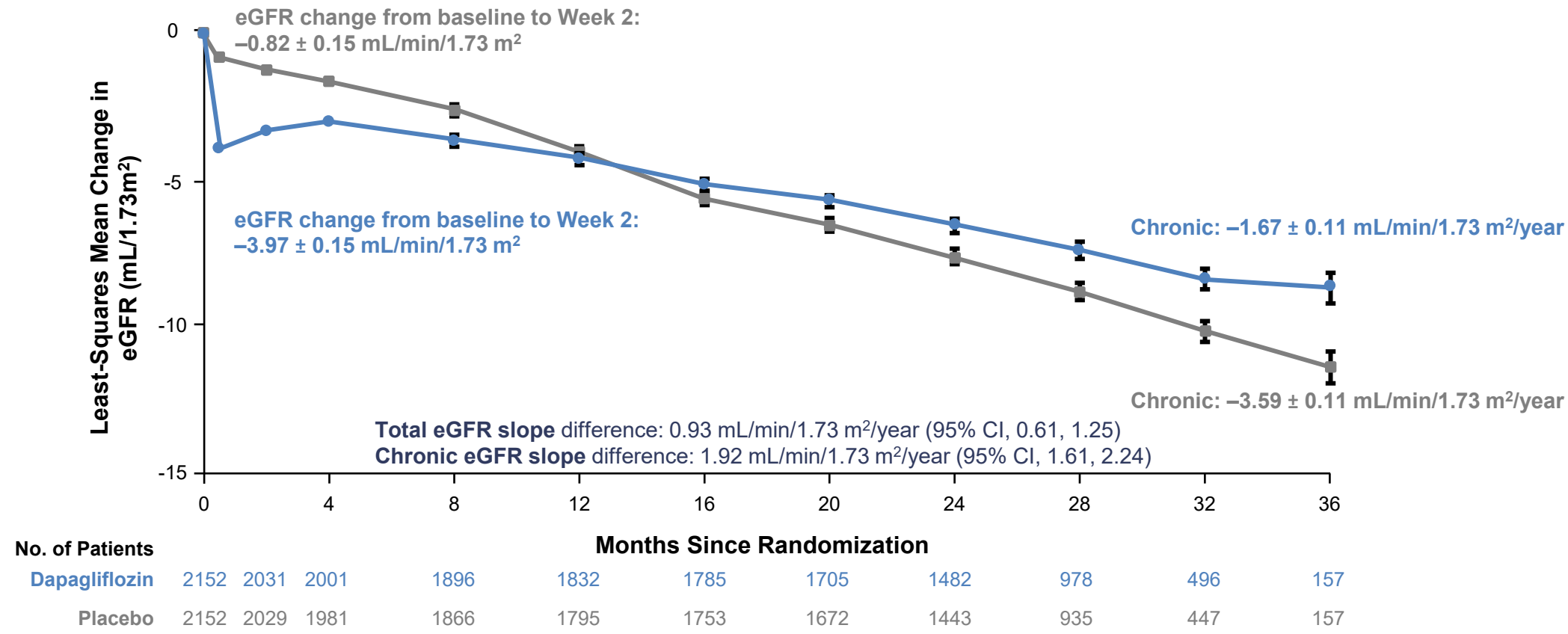
Exploratory Composite Outcome: Chronic Dialysis, Kidney Transplantation, or Renal Death[1,2]



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

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282

Change from Baseline in eGFR[1,2]



BL = baseline; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Toto R. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020

Safety

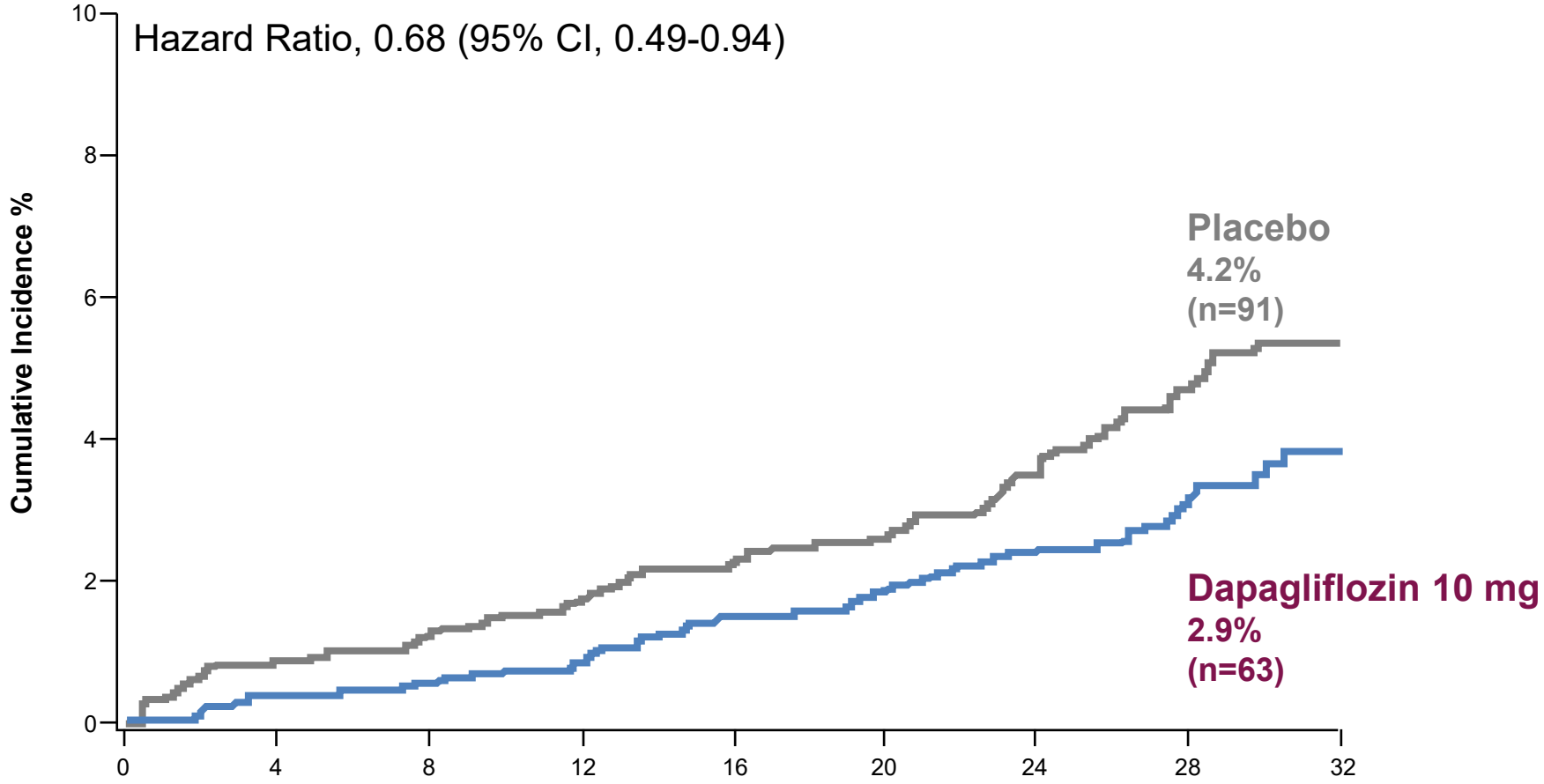
Safety Outcomes[1]

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

Cumulative Incidence of AKI



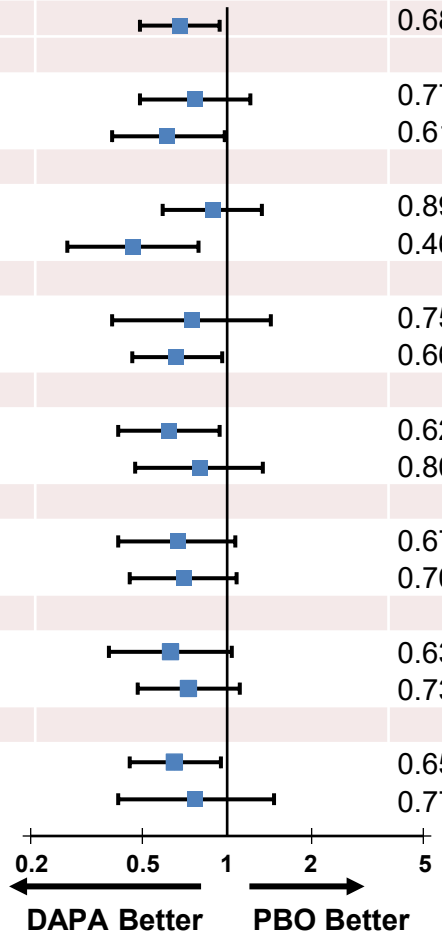
N at Risk									
Dapagliflozin 10 mg	2152	2031	2017	1998	1965	1881	1484	1000	375
Placebo	2152	2015	1989	1958	1930	1850	1445	969	358

AKI = acute kidney injury; CI = confidence interval

Heerspink HJL et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

AKI by Baseline Subgroups

	Events/100 patient years		Hazard ratio (95% CI)	P value for interaction
	DAPA	PBO		
Overall	1.4	2.0	0.68 (0.49-0.94)	
Age (years)				**0.45**
≤65	1.3	1.7	0.77 (0.49-1.21)	
>65	1.5	2.4	0.61 (0.39-0.98)	
Gender				**0.05**
Male	1.4	1.6	0.89 (0.59-1.33)	
Female	1.3	2.8	0.46 (0.27-0.79)	
T2D				**0.77**
No	1.1	1.5	0.75 (0.39-1.43)	
Yes	1.5	2.2	0.66 (0.46-0.96)	
eGFR				**0.49**
<45 mL/min/1.73 m^2	1.4	2.3	0.62 (0.41-0.94)	
≥45 mL/min/1.73 m^2	1.3	1.7	0.80 (0.47-1.34)	
UACR				**0.86**
≤1000 mg/g	1.2	1.8	0.67 (0.41-1.07)	
>1000 mg/g	1.6	2.2	0.70 (0.45-1.08)	
Diuretic use				**0.66**
No	1.0	1.5	0.63 (0.38-1.04)	
Yes	1.9	2.6	0.73 (0.48-1.11)	
Heart failure				**0.71**
No	1.1	1.7	0.65 (0.45-0.95)	
Yes	3.3	4.3	0.77 (0.41-1.47)	



AKI = acute kidney injury; CI = confidence interval; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio

Heerspink HJL et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

Summary of Dapagliflozin Use in CKD

Summary

- **DAPA-CKD[1],** the first dedicated renal outcomes trial to assess the efficacy and safety of an SGLT-2 inhibitor in patients with CKD with and without T2D, demonstrated:

39% RRR	**44%** RRR	**29%** RRR	**31%** RRR
for the primary composite endpoint (≥50% sustained decline in eGFR, ESKD, renal or CV death)	for the renal composite (≥50% sustained decline in eGFR, ESKD, or renal death)	for the composite of CV death or hospitalization for heart failure	all-cause mortality

- Consistent treatment effect in patients with CKD across major subgroups including in patients **with and without T2D,** and by baseline eGFR and UACR categories
- Dapagliflozin was well-tolerated for the treatment of CKD (in patients with and without T2D) and data **confirm the known safety profile**
- **DAPA-CKD** builds upon the evidence for dapagliflozin in the prevention of hHF and worsening of renal disease in **DECLARE[2]** and reduction in the risk of worsening HF and CV death in **DAPA-HF[3]**

CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; hHF = hospitalization for heart failure; RRR = relative risk reduction; SGLT-2 = sodium glucose co-transporter 2; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446. 2. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357. 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008.

DAPA-CKD Expands the Cardiorenal Benefit of Dapagliflozin to Patients with CKD

	DECLARE TIMI-58	DAPA-HF	DAPA-CKD
	N = 17,160[1]	N = 4744[2]	N = 4304[3,4]
Patient Population	**ASCVD (~40%) or MRF (~60%) eGFR ≥60 mL/min/1.73m²**	**HFrEF eGFR ≥30 mL/min/1.73m²**	**CKD eGFR ≥25 to ≤75 mL/min/1.73m²**
Glycemic Status	**With T2D**	**With (45%) or Without (55%) T2D**	**With (68%) or Without (32%) T2D**
Mean eGFR	**85.2 mL/min/1.73m²**	**66 mL/min/1.73m²**	**43 mL/min/1.73m²**
Primary Endpoint	• **hHF or CV death** 0.83 (0.73, 0.95) p=0.005	• **CV death or worsening HF (hHF, or urgent hHF visit)** 0.74 (0.65, 0.85) p<0.001	• **≥50% eGFR Decline, ESKD, or Renal or CV Death** 0.61 (0.51-0.72) p=0.000000028
Key Endpoint	• **eGFR decrease ≥40% to <60, ESKD or renal death** 0.53 (0.43, 0.66) p<0.0001[a]	• **≥50% sustained decline in eGFR, ESKD or renal death** 0.71 (0.44, 1.16) p=0.17	• **CV death or hHF** 0.71 (0.55, 0.92) p=0.0089

CV

Renal

[a] Because the trial met only one of its dual primary composite outcomes for superiority (CV death or hospital admission for heart failure), all other analyses of additional outcomes should be considered hypothesis generating only.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; T2D = type 2 diabetes.

1. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357. 2. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008. 3. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020; 4. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

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AF = atrial fibrillation; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; FSGS = focal segmental glomerulosclerosis; HbA1c = glycated hemoglobin; HF = heart failure; IgA = immunoglobulin A; MRA = mineralocorticoid receptor antagonist; PAD = peripheral artery disease; T2D = type 2 diabetes.

DAPA-CKD Subgroup Analysis
Etiology

In a pre-specified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to the underlying cause of kidney disease

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

Baseline Characteristics by Underlying Cause of Kidney Disease

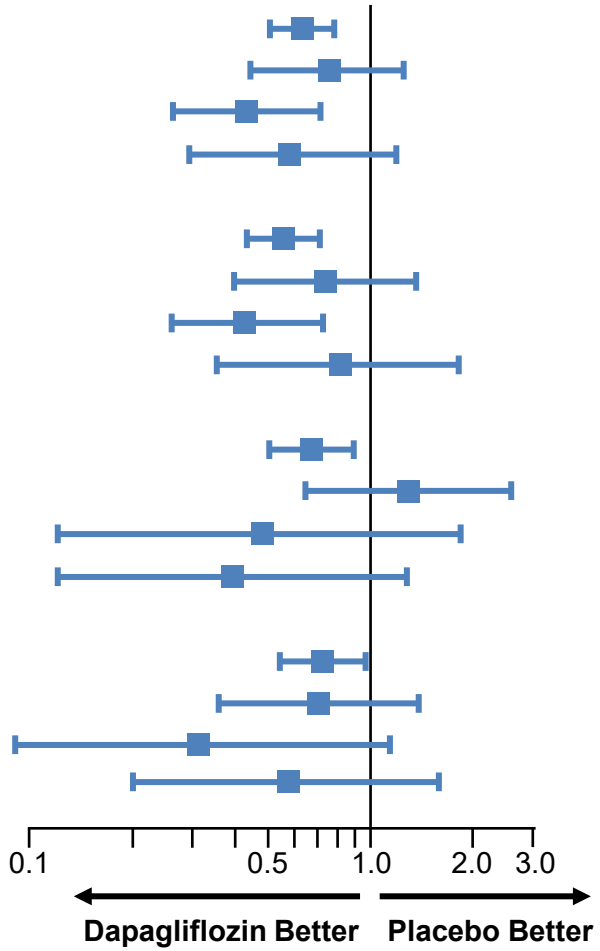
Characteristic	Diabetic Nephropathy		Ischemic / Hypertensive Nephropathy		Glomerulonephritides		Other / Unknown	
	DAPA (n=1271)	PBO (n=1239)	DAPA (n=324)	PBO (n=363)	DAPA (n=343)	PBO (n=352)	DAPA (n=214)	PBO (n=198)
Age, years, mean	64.2	65.0	64.2	63.1	51.9	51.7	59.6	58.4
Sex, female, %	34.2	33.0	26.9	27.5	34.1	38.9	32.7	35.4
Race, %								
White	51.7	54.6	54.6	54.5	48.1	50.0	58.4	58.6
Black or African-American	5.2	4.0	7.7	8.0	1.7	0.9	3.3	3.0
Asian	32.2	30.1	32.1	30.0	47.2	46.6	34.6	36.4
Other	10.9	11.4	5.6	7.4	2.9	2.6	3.7	2.0
Weight, kg, mean	82.9	83.4	82.7	83.5	77.2	77.2	78.1	79.6
Blood pressure, mmHg, mean	139/76	140/76	138/80	140/80	129/79	129/78	134/79	135/81
eGFR, mL/min/1.73m^2, mean	44.2	43.5	42.0	42.0	42.9	42.8	40.2	41.7
UACR, mg/mmol, median	119.3	117.3	90.5	80.3	110.2	110.9	89.8	95.0
mg/g	1056	1038	801	711	976	981	795	841

DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo; UACR = urinary albumin to creatine ratio.

Wheeler DC. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

DAPA-CKD Primary and Secondary Outcomes by Underlying Cause of Kidney Disease

	Dapagliflozin Events	Placebo Events	Hazard Ratio (95% CI)	p-value Interaction
Primary outcome[a]				
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)	
Glomerulonephritides	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[b]				
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)	
Glomerulonephritides	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 heart failure				
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)	
Glomerulonephritides	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)	
Glomerulonephritides	3/343	11/352	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	0.57 (0.20, 1.61)	



[a]Sustained ≥50% eGFR decline, ESKD, renal or CV death; [b]Sustained ≥50% eGFR decline, ESKD, renal death; CKD = chronic kidney disease; CV=cardiovascular;
Toto R. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

Adverse Events by Kidney Disease Diagnosis at Baseline

Etiology, n[1]	Dapagliflozin 10 mg (n=2149)	Placebo (n=2149)	Odds Ratio (95% CI)	P-value for interaction
Diabetic nephropathy	1269	1239		
Hypertensive CKD	324	362		
Glomerulonephritis	343	351		
IgA nephropathy[2]	137	133		
FSGS[3]	53	61		
Other / Unknown	213	197		
Outcome, n (%)[1]				
Discontinuation due to adverse event, n (%)				0.0352
Diabetic nephropathy	71 (5.6)	82 (6.6)	0.84 (0.60, 1.16)	
Hypertensive CKD	17 (5.2)	18 (5.0)	1.06 (0.53, 2.10)	
Glomerulonephritis	16 (4.7)	20 (5.7)		
IgA nephropathy[2]	6 (4.4)	7 (5.3)	0.81 (0.41, 1.59)	
FSGS[3]	4 (7.5)	4 (6.6)		
Other / Unknown	14 (6.6)	3 (1.5)	4.55 (1.46, 19.96)	
Any serious adverse event, n (%)[a]				0.1363
Diabetic nephropathy	427 (33.6)	492 (39.7)	0.77 (0.65, 0.91)	
Hypertensive CKD	94 (29.0)	108 (29.8)	0.96 (0.69, 1.34)	
Glomerulonephritis	64 (18.7)	91 (25.9)		
IgA nephropathy[2]	22 (16.1)	34 (25.6)	0.66 (0.46, 0.94)	
FSGS[3]	9 (17.0)	19 (31.1)		
Other / Unknown	48 (22.5)	38 (19.3)	1.22 (0.76, 1.97)	

[a]Includes death.

CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis; IgA = immunoglobulin A.

1. Wheeler DC et al. Article and supplementary appendix. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Heerspink HJL et al. Presented at: WCN; April 16-19, 2021; Virtual;
3. Wheeler DC et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

Summary

- In this pre-specified analysis, renal, CV, and mortality beneficial effects of dapagliflozin were consistent with the overall effect regardless of underlying cause of kidney disease
- Dapagliflozin was well tolerated; the safety profile was consistent across underlying causes of kidney disease

Wheeler DC. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

DAPA-CKD Subgroup Analysis
IgA Nephropathy

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed in patients with CKD due to IgA Nephropathy

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Baseline Characteristics in Patients with IgA Nephropathy

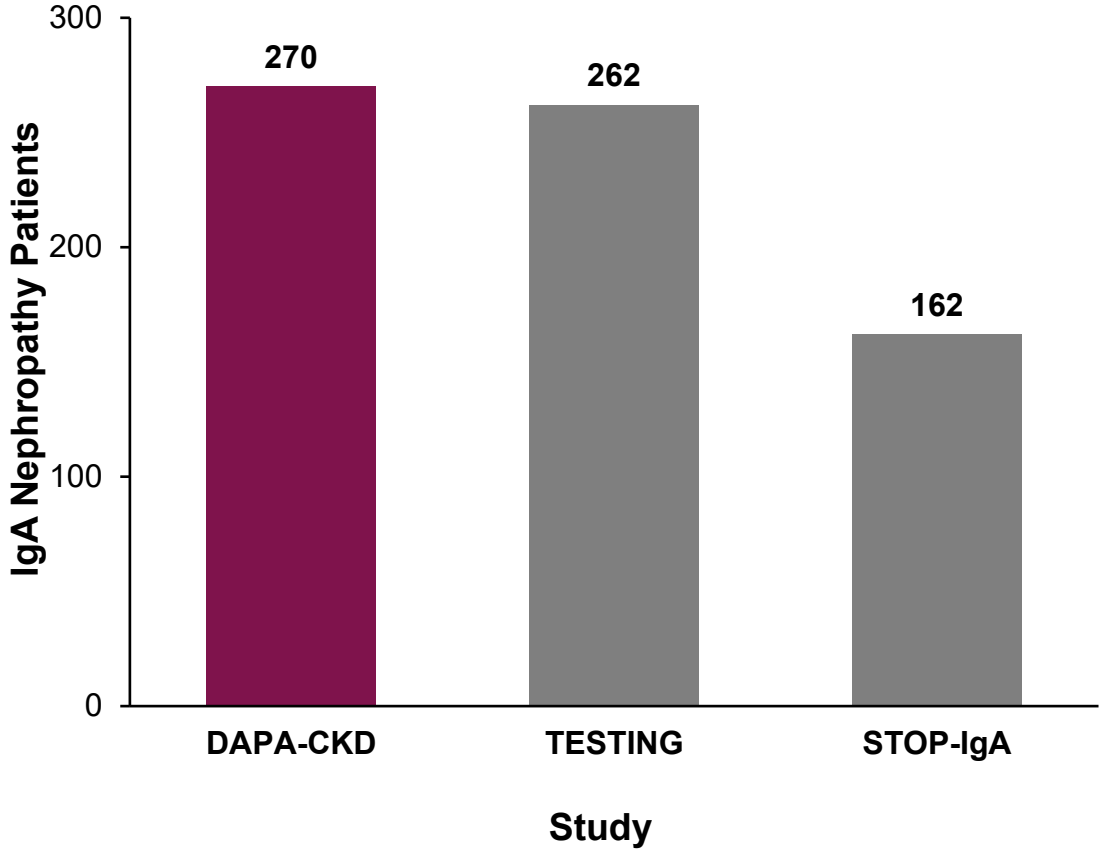
Characteristic	Dapagliflozin (n=137)	Placebo (n=133)	Total (n=270)
Age, years, mean	52	50	51
Sex, female, %	32	33	33
Race, %			
White	39	41	40
Black or African-American	0	1	0
Asian	60	58	59
Other	1	1	1
Weight, kg, mean	75	79	77
Systolic/diastolic blood pressure, mmHg, mean	128/79	127/80	127/79
eGFR, mL/min/1.73m^2, mean	44	43	44
UACR, mg/mmol, median	100.6	102.0	101.7
UACR ≤113 mg/mmol, %	56	55	56
UACR >113 mg/mmol, %	44	45	44
Type 2 diabetes, %	18	11	14
IgA nephropathy confirmed by previous biopsy, %	94	94	94

IgA = immunoglobulin A; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio

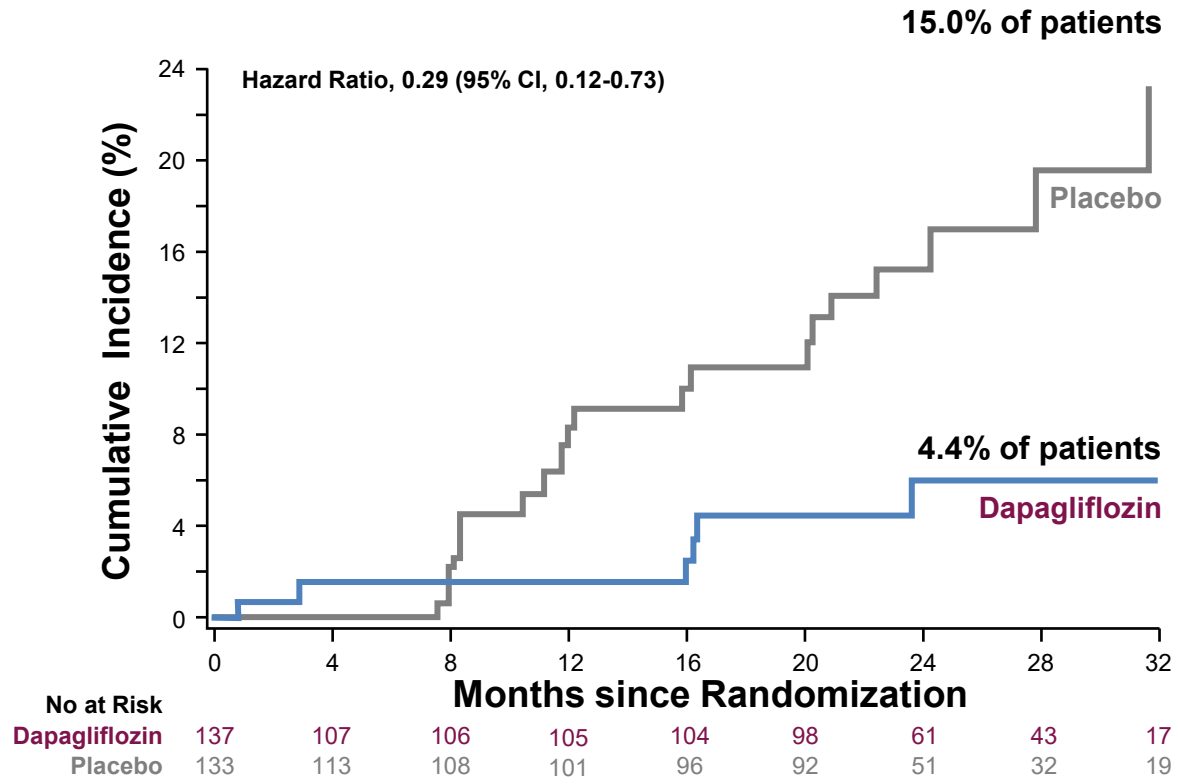
Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Further Exploring the Effect of Dapagliflozin by Causes Of Kidney Disease in DAPA-CKD – IgA Nephropathy

Number of participants with IgA nephropathy in clinical trials[1]



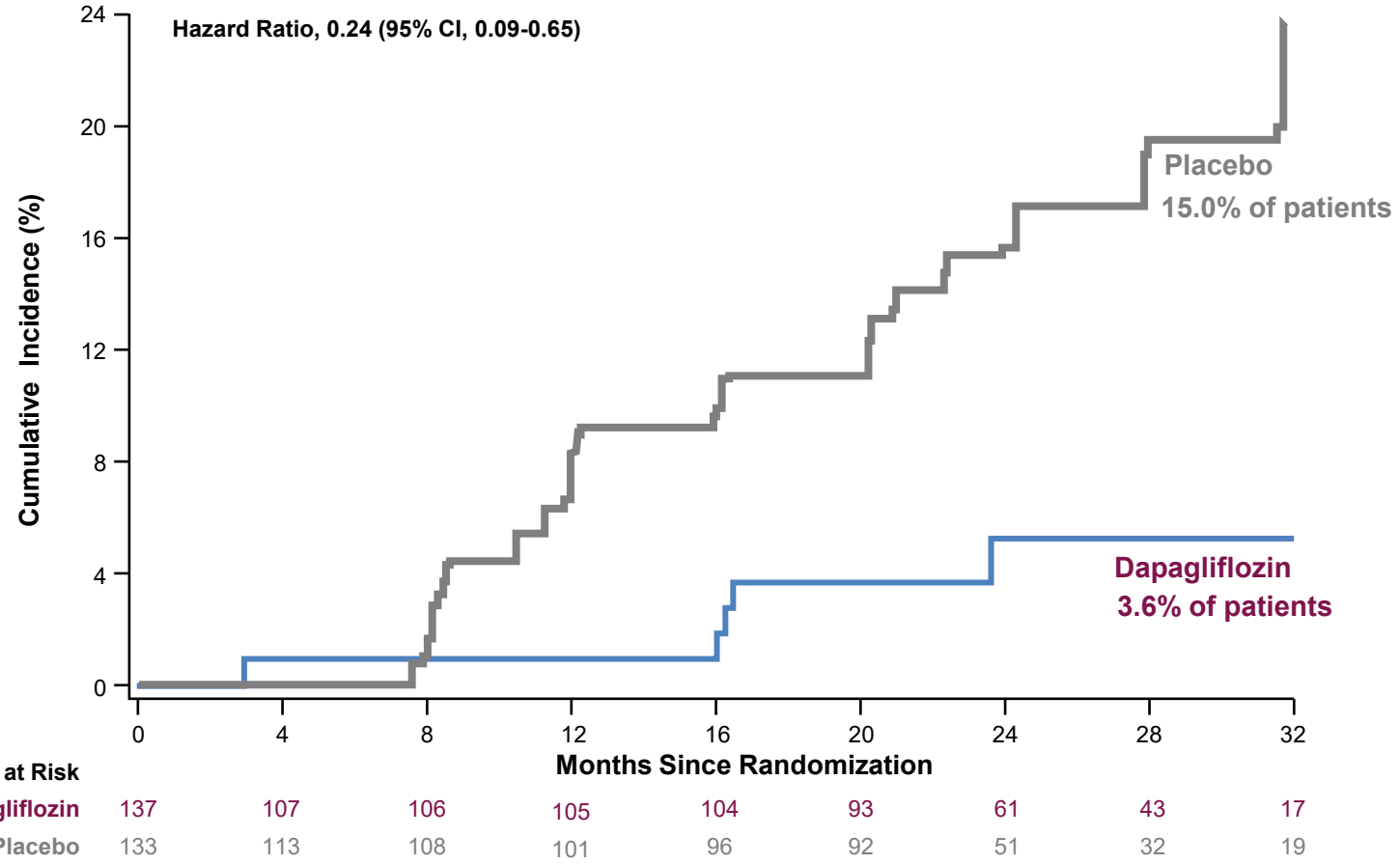
Primary outcome in participants with IgA nephropathy[2,3]



CKD = chronic kidney disease; IgA = immunoglobulin A

1. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711; 2. Wheeler DC et al. Article and supplementary appendix. *Lancet Diabetes Endocrinol.* 2021;9:22–31;
3. Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Secondary Kidney-Specific Composite Outcome (Sustained ≥50% eGFR Decline, ESKD, or Kidney Death[a]) in Patients With IgA Nephropathy



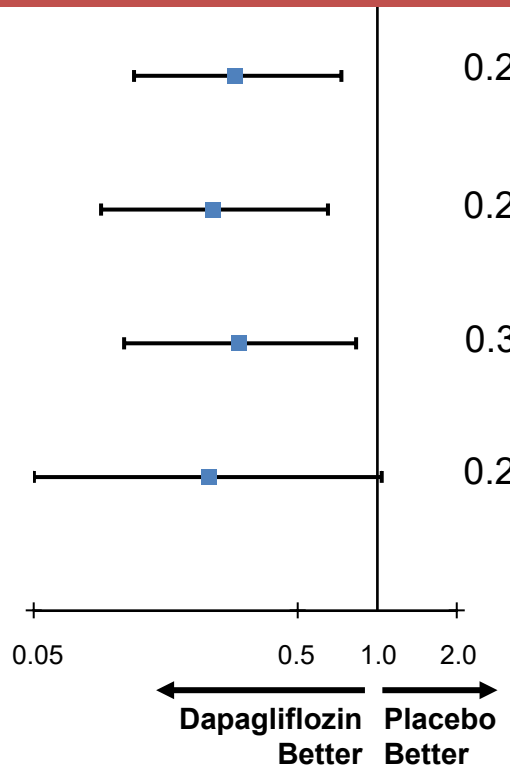
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and kidney transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Kidney death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; IgA = immunoglobulin A; T2D = type 2 diabetes.

1. Wheeler DC et al. *Kidney Int*. 2021;100:215-224; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Key Endpoints in Patients with IgA Nephropathy

	Dapagliflozin	Placebo	Dapagliflozin	Placebo		
	No. of patients/total no.		Events/100 patient-years		Hazard Ratio (95% CI)	p-value
Primary endpoint[a]	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	0.005
Kidney-specific endpoint[b]	5/137	20/133	2.1	8.8	0.24 (0.09, 0.65)	0.002
ESKD[c]	5/137	16/133	2.1	6.9	0.30 (0.11, 0.83)	0.014
Composite endpoint of chronic dialysis, kidney transplant and kidney death	2/137	10/133	0.8	4.0	0.23 (0.05, 1.04)	NC



[a]Composite of sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney or cardiovascular cause; [b]Composite of sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney cause; [c]Maintenance dialysis for ≥28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after 28 days.

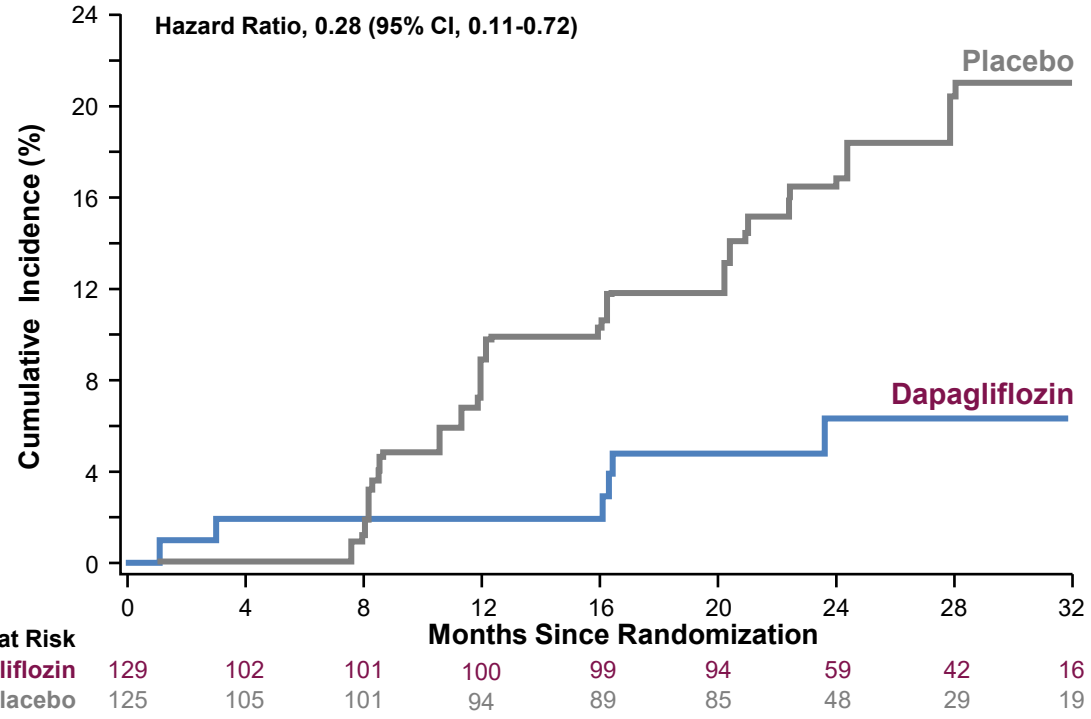
eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; IgA = immunoglobulin A.

Heerspink HJL et al. Presented at: WCN; April 16-19, 2021; Virtual.

Outcomes in Patients with IgA Nephropathy Confirmed With a Biopsy

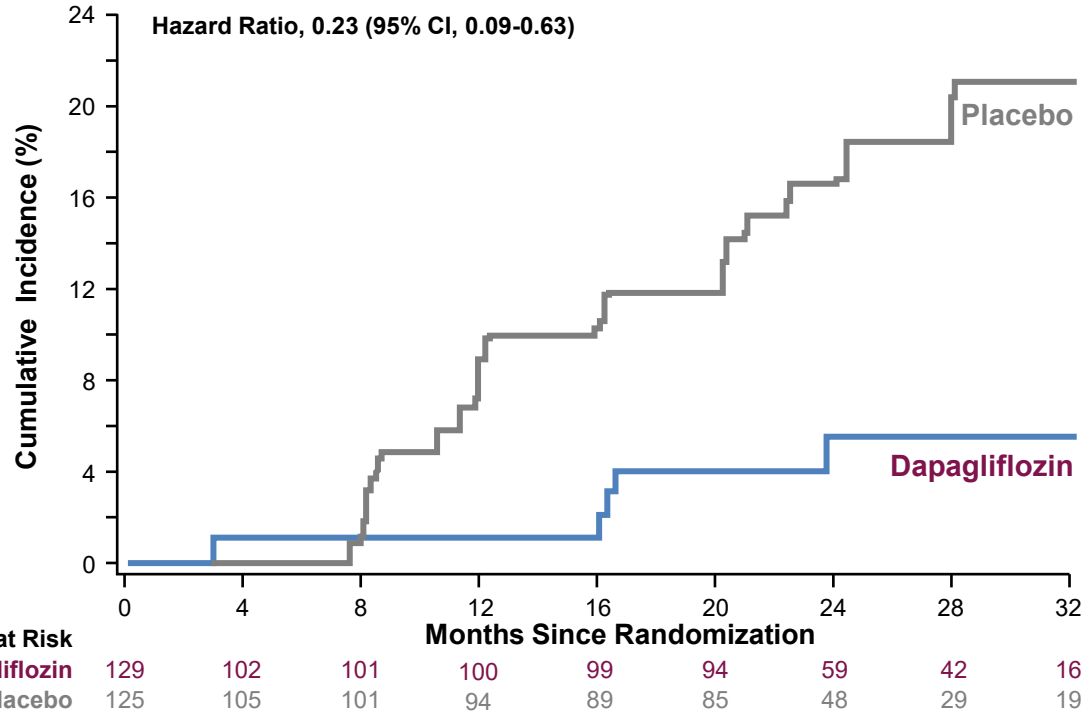
Diagnosis of IgA nephropathy was confirmed by previous biopsy in 254 (94%) patients

Primary Outcome[a]



No at Risk									
Dapagliflozin	129	102	101	100	99	94	59	42	16
Placebo	125	105	101	94	89	85	48	29	19

Kidney-specific Outcome[b]



No at Risk									
Dapagliflozin	129	102	101	100	99	94	59	42	16
Placebo	125	105	101	94	89	85	48	29	19

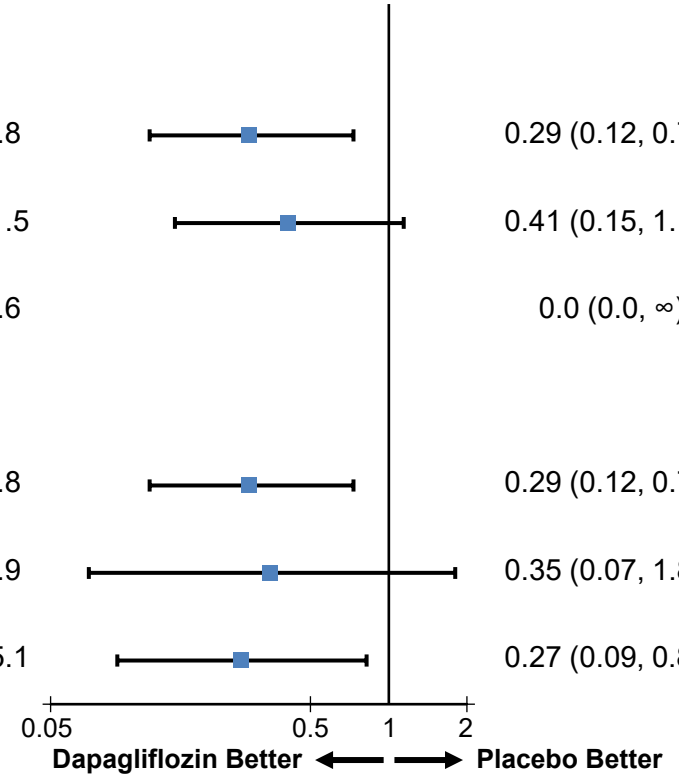
[a]Composite of sustained ≥50% decline in eGFR, onset of ESKD[c], or death from a kidney or cardiovascular cause; [b]Composite of sustained ≥50% decline in eGFR, onset of ESKD[c], or death from a kidney cause; [c]Maintenance dialysis for ≥28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after 28 days.

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; IgA = immunoglobulin A.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Primary composite endpoint by pre-specified baseline eGFR and UACR subgroups in patients with IgA nephropathy

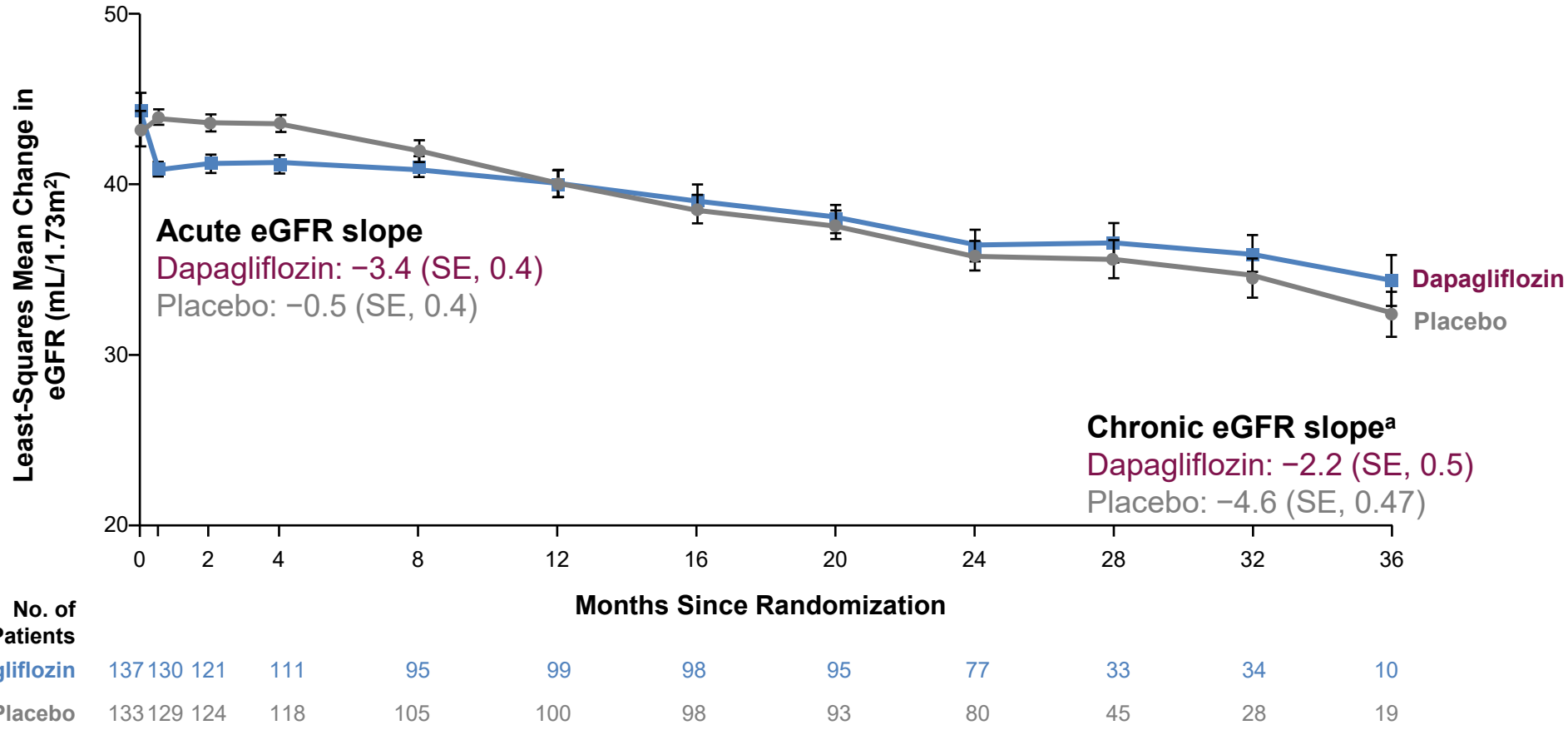
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	Absolute risk difference (95% CI)
	No. of participants/total no.		Events/100 patient years			
eGFR						
Overall	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
<45 mL/min/1.73m^2	6/76	12/70	4.8	11.5	0.41 (0.15, 1.14)	-9.2 (-20.0, 1.5)
≥45 mL/min/1.73m^2	0/61	8/63	0.0	6.6	0.0 (0.0, ∞)	NC
UACR						
Overall	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
≤113 mg/mmol (1000 mg/g)	2/77	5/73	1.5	3.9	0.35 (0.07, 1.80)	-4.3 (-11.0, 2.5)
>113 mg/mmol (1000 mg/g)	4/60	15/60	4.0	15.1	0.27 (0.09, 0.82)	-18.3 (-31.0, -5.7)



eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; NC = not calculable; UACR = urinary albumin-to-creatinine ratio

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Changes Over Time in eGFR Trajectory in Patients With IgA Nephropathy



No. of Patients											
Dapagliflozin	137	130	121	111	95	99	98	95	77	33	34	10
Placebo	133	129	124	118	105	100	98	93	80	45	28	19

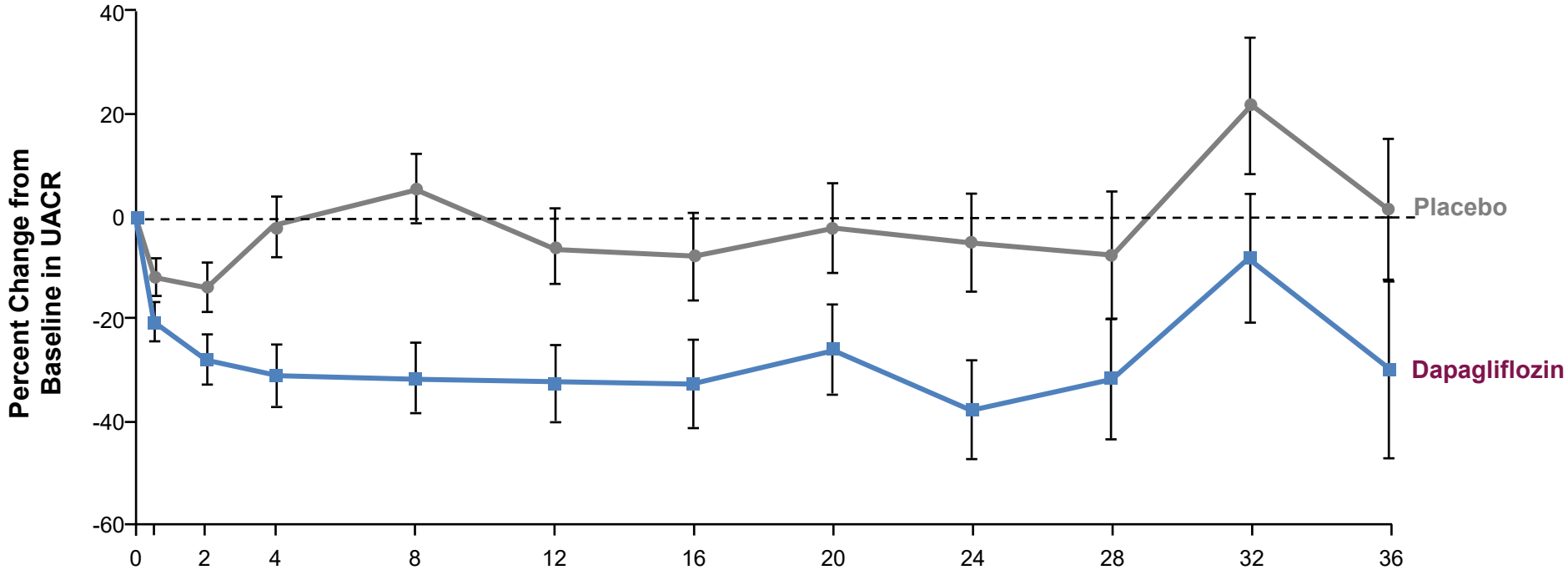
Error bars represent standard error.

[a]Chronic eGFR slope defined as annual mean change with DAPA vs PBO from week 2.

eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; SE = standard error.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Changes Over Time in UACR in Patients With IgA Nephropathy[a]



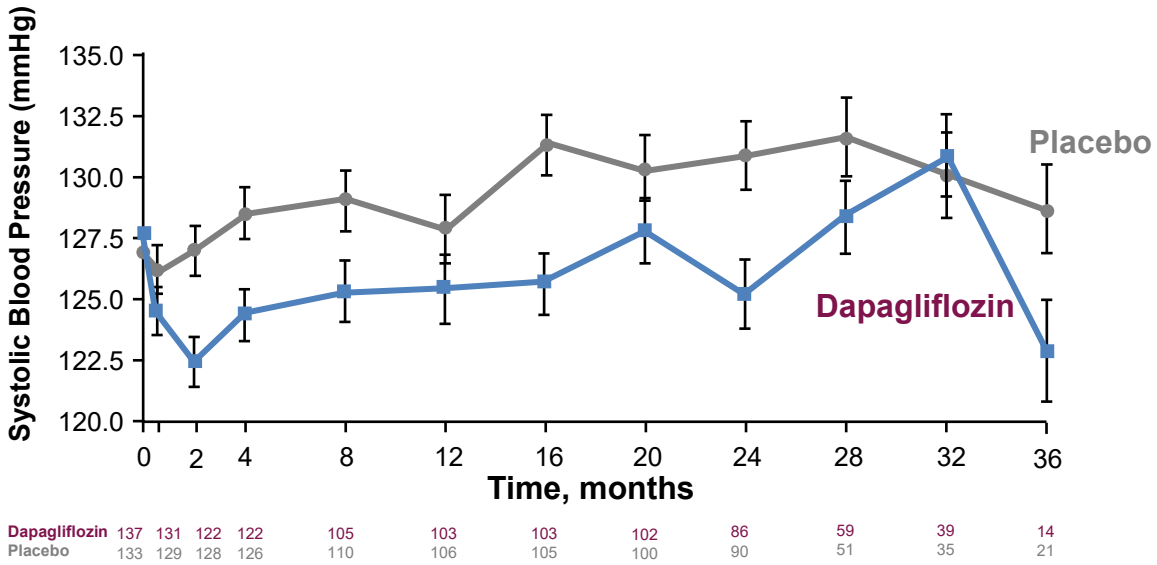
No. of Patients												
Dapagliflozin	137	130	121	111	95	99	98	95	77	53	34	10
Placebo	133	129	124	118	105	100	98	93	80	45	28	19

Mean difference[b]: −26 (95% CI, −37 to −14; p<0.001)

[a]Error bars represent standard error; [b]Dapagliflozin versus placebo.
eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; UACR = urinary albumin-to-creatinine ratio.
Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

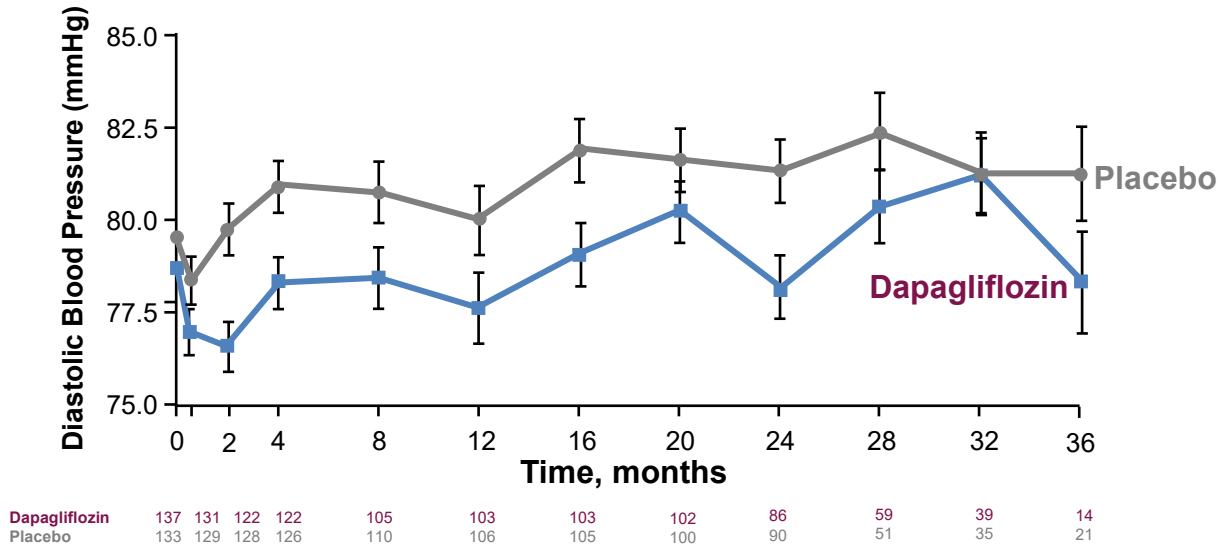
Changes Over Time in Blood Pressure in Patients With IgA Nephropathy

Change in systolic blood pressure over time[a]



Mean difference[b]: -3.5 (95% CI, -5.7 to -1.3; p=0.002)

Change in diastolic blood pressure over time[a]



Mean difference[b]: -2.2 (95% CI, -3.7 to -0.8; p=0.003)

[a]Error bars represent standard error; [b]Dapagliflozin versus placebo.
eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A.
Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Safety outcomes

Safety outcomes	Dapagliflozin (n=137)	Placebo (n=133)
Adverse events leading to discontinuation of the study drug, n (%)	6 (4.4)	7 (5.3)
Serious adverse event,[a] n (%)	22 (16.1)	34 (25.6)

[a]Includes death.
IgA = immunoglobulin A.
Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Summary

- In patients with IgA nephropathy, the numeric reduction in the relative risk of the primary composite endpoint and renal specific composite endpoint with dapagliflozin was consistent with the overall results
- Dapagliflozin was well tolerated; the proportion of patients with serious adverse events did not vary between treatment groups when divided by underlying cause of CKD

CKD = chronic kidney disease; CV = cardiovascular; ESKD = end stage kidney disease; FSGS = focal segmental glomerulosclerosis; IgA = immunoglobulin A.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

DAPA-CKD Subgroup Analysis
FSGS

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed in patients with CKD due to FSGS

CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis.
Wheeler DC et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

Baseline Characteristics in the FSGS Subgroup

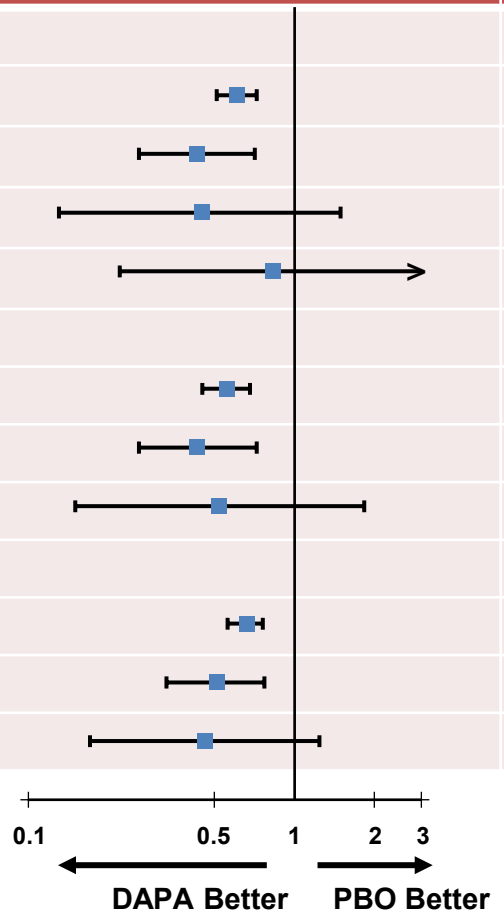
Characteristic	Dapagliflozin (N=53)	Placebo (N=62)	Total (N=115)
Age, years, mean	52	55	54
Sex, female, %	28	36	32
Race, %			
White	64	52	57
Black or African-American	9	3	6
Asian	17	37	28
Other	9	8	9
Weight, kg, mean	91	83	87
Blood pressure, mmHg, mean	130/78	130/77	130/77
eGFR, mL/min/1.73m^2, mean	39.8	43.1	41.6
UACR, mg/g, median	1107	1413	1283
Type 2 diabetes, %	11	26	19
Baseline medications, %			
ACE inhibitor	38	34	36
ARB	62	63	63

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FSGS = focal segmental glomerulosclerosis; UACR = urinary albumin-to-creatinine ratio.

Wheeler DC et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual

Outcomes in Patients With FSGS[1]

	DAPA (n/N)	PBO (n/N)	Hazard ratio (95% CI)
Primary composite outcome			
Overall[2]	197/2152	312/2152	0.61 (0.51, 0.72)
Glomerulonephritis[3]	22/343	49/352	0.43 (0.26, 0.71)
FSGS	4/53	9/62	0.45 (0.13, 1.49)
Biopsy-confirmed FSGS	4/45	7/59	0.83 (0.22, 3.12)
Kidney-specific composite outcome			
Overall[2]	142/2152	243/2152	0.56 (0.45, 0.68)
Glomerulonephritis[3]	21/343	46/352	0.43 (0.26, 0.72)
FSGS	4/53	7/62	0.52 (0.15, 1.83)
Composite of sustained ≥40% eGFR decline, ESKD or renal or CV death			
Overall	287/2152	414/2152	0.66 (0.56, 0.76)
Glomerulonephritis	34/343	63/352	0.51 (0.33, 0.77)
FSGS	6/53	13/62	0.46 (0.17, 1.24)



CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis; PBO = placebo.

1. Wheeler DC et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual; 2. Heerspink HJL et al. *N Engl J Med*. 2020;383:1436-1446. 3. Wheeler DC et al. *Lancet Diabet Endocrinol*. 2021;9:22-31.

Safety outcomes

Safety outcomes	Dapagliflozin (n=53)	Placebo (n=61)
Adverse events leading to discontinuation of the study drug, n (%)	4 (7.5)	4 (6.6)
Any serious adverse event,[a] n (%)	9 (17.0)	19 (31.1)

[a]Includes death.

Wheeler DC et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual

Summary

- In patients with FSGS, the numeric reduction in the relative risk of the primary composite endpoint and renal specific composite endpoint with dapagliflozin was consistent with the overall results
- Dapagliflozin was well tolerated; the proportion of patients with serious adverse events did not vary between treatment groups when divided by underlying cause of CKD

CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis.

Wheeler DC et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual

DAPA-CKD Subgroup Analysis
Stage 4 CKD

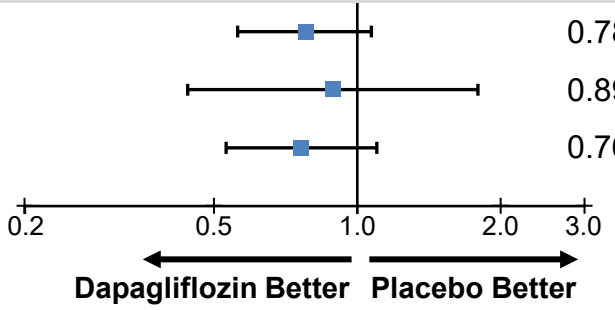
In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed by stage of CKD, including Stage 4 CKD (<30 ml/min/1.73m^2)

CKD = chronic kidney disease.

Chertow GM et al. Presented at: WCN; April 16-19, 2021; Virtual.

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)	



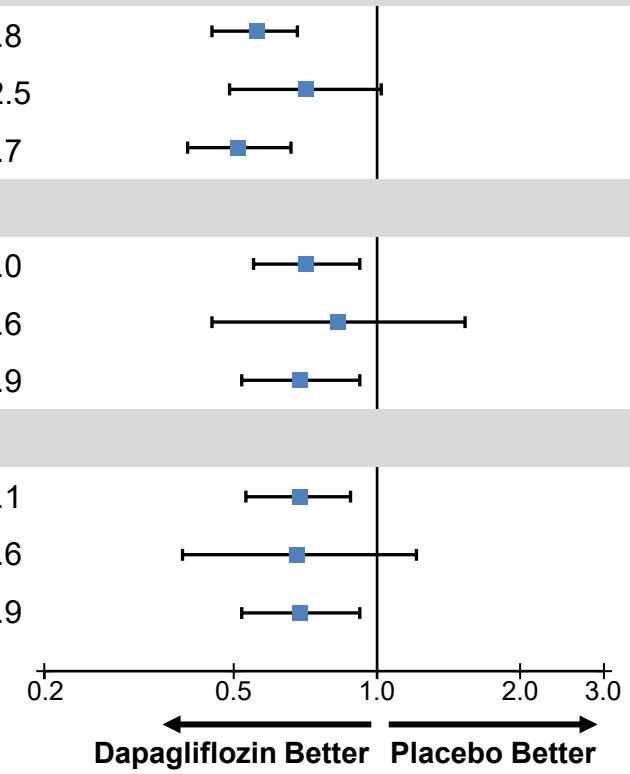
NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2

CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.

Chertow GM et al. Published online ahead of print, July 16, 2021. *J Am Soc Nephrol*. 2021. DOI: 10.1681/ASN.2021020167

Secondary Outcomes According to CKD Stage

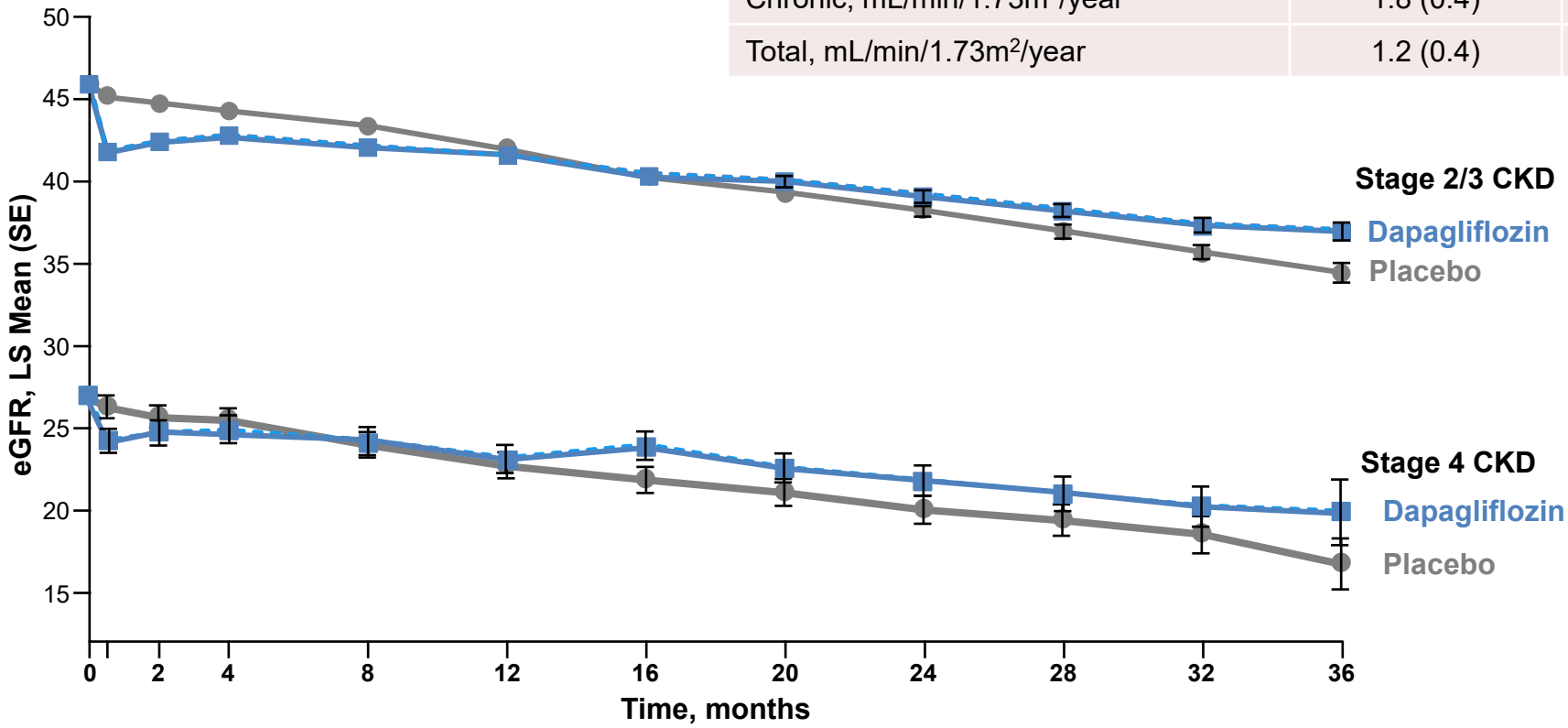
	Dapagliflozin	Placebo	Dapagliflozin	Placebo		Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients/ total no.		Events/100 patient-years				
Kidney composite outcome: ≥50% eGFR decline, ESKD, or kidney death							
Overall	142/2152	243/2152	3.3	5.8		0.56 (0.45, 0.68)	
Stage 4	49/293	73/331	9.2	12.5		0.71 (0.49, 1.02)	0.13
Stage 2/3	93/1859	170/1821	2.5	4.7		0.51 (0.40, 0.66)	
CV death or heart failure hospitalization							
Overall	100/2152	138/2152	2.2	3.0		0.71 (0.55, 0.92)	
Stage 4	18/293	24/331	2.9	3.6		0.83 (0.45, 1.53)	0.63
Stage 2/3	82/1859	114/1821	2.0	2.9		0.69 (0.52, 0.92)	
All-cause death							
Overall	101/2152	146/2152	2.2	3.1		0.69 (0.53, 0.88)	
Stage 4	19/293	31/331	3.0	4.6		0.68 (0.39, 1.21)	0.95
Stage 2/3	82/1859	115/1821	2.0	2.9		0.69 (0.52, 0.92)	



NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2.
CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.
Chertow GM et al. Published online ahead of print, July 16, 2021. *J Am Soc Nephrol*. 2021. DOI: 10.1681/ASN.2021020167

eGFR Decline Over the Study by Baseline CKD Stage

Between slope difference[a] (SE)	Stage 4 CKD	Stage 2/3 CKD
Acute, mL/min/1.73m^2/2 weeks	–1.4 (0.5)	–2.6 (0.2)
Chronic, mL/min/1.73m^2/year	1.8 (0.4)	1.9 (0.2)
Total, mL/min/1.73m^2/year	1.2 (0.4)	0.9 (0.2)



NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2.

[a]dapagliflozin vs placebo.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

Chertow GM et al. Published online ahead of print, July 16, 2021. *J Am Soc Nephrol*. 2021. DOI: 10.1681/ASN.2021020167

Safety Outcomes According to CKD Stage

Safety outcomes, %	Stage 4 CKD		Stage 2/3 CKD	
	Dapagliflozin (n=293)	Placebo (n=331)	Dapagliflozin (n=1859)	Placebo (n=1821)
Discontinuation due to adverse event	9.6	10.9	4.8	4.8
Any serious adverse event[a]	34.5	41.7	28.7	32.5
Adverse event of interest				
Amputation	1.0	1.2	1.7	1.9
Definite or probable DKA	0	0.3	0	0.1
Fracture	3.8	4.5	4.0	3.0
Renal-related adverse event	14.7	13.3	6.0	7.9
Major hypoglycemia	0.7	2.4	0.6	1.1
Volume depletion	4.8	4.5	6.1	4.1

NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2.
[a]Includes death.
CKD = chronic kidney disease; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate.
Chertow GM et al. Published online ahead of print, July 16, 2021. *J Am Soc Nephrol*. 2021. DOI: 10.1681/ASN.2021020167

Summary

- In this pre-specified analysis in patients with advanced CKD (Stage 4 CKD), the results were consistent with the overall effect regardless of underlying stage of kidney disease
- Dapagliflozin attenuated progressive loss of eGFR in patients with Stage 4 CKD, consistent with those in Stage 2/3 CKD
- Dapagliflozin was well tolerated; the proportion of patients with serious adverse events was similar in patients with Stage 4 CKD and Stage 2/3 CKD.
  - In patients with Stage 4 CKD, events of volume depletion and renal-related adverse events were numerically higher with dapagliflozin

CKD = chronic kidney disease; CV = cardiovascular; egFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

Chertow GM et al. Published online ahead of print, July 16, 2021. *J Am Soc Nephrol*. 2021. DOI: 10.1681/ASN.2021020167

DAPA-CKD Subgroup Analysis
Baseline Albuminuria

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed for the primary and secondary outcomes stratified by UACR at baseline (≤1000 mg/g, >1000 to ≤3500 mg/g, >3500 mg/g)

UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

Patient Characteristics by Baseline Albuminuria

Characteristic	UACR Categories ≤113 mg/mmol (1000 mg/g) (n=2225)	>113 to ≤395.5 mg/mmol (>1000 to ≤3500 mg/g) (n=1764)	>395.5 mg/mmol (3500 mg/g) (n=315)	P value[a]
Age, years, mean	62.7	61.0	60.1	<0.001
Female sex, %	32.5	32.9	38.4	0.11
Race, %				<0.001
White	55.6	51.9	43.5	
Black or African American	4.7	4.2	3.8	
Asian	34.2	34.5	31.1	
Other	5.5	9.3	21.6	
Blood pressure, mmHg, mean	134/76	139/79	145/80	<0.001
eGFR, mL/min/1.73m^2, mean	44.0	42.5	40.6	<0.001
UACR, mg/mmol, median	55.1	197.1	466.4	<0.001
Mg/g	488	1744	4127	
HbA1c, %, mean	7.0	7.1	7.6	<0.001
Type 2 diabetes, %	64.4	68.2	85.4	<0.001
History of CVD, %	36.6	37.9	40.0	0.43

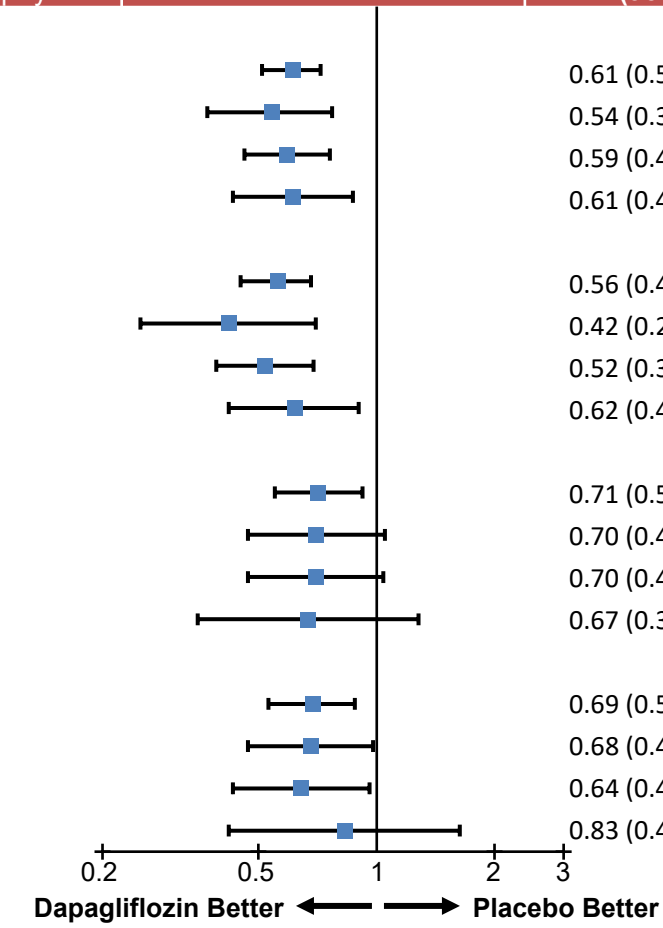
[a]Across the 3 strata of baseline UACR.

CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

Primary and Secondary Outcomes by Baseline Albuminuria

	Dapagliflozin Events/100 pt-yrs	Placebo Events/100 pt-yrs	Hazard Ratio (95% CI)	Interaction P-Value
Primary outcome: eGFR decline ≥50%, ESKD, or kidney or CV death				
Overall	4.6	7.5	0.61 (0.51 to 0.72)	
UACR ≤113 mg/mmol (1000 mg/g)	1.9	3.7	0.54 (0.37 to 0.77)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	5.6	9.3	0.59 (0.46 to 0.76)	0.93
UACR >395.5 mg/mmol (3500 mg/g)	18.7	31.2	0.61 (0.43 to 0.87)	
Secondary outcome: eGFR decline ≥50%, ESKD, or kidney death				
Overall	3.3	5.8	0.56 (0.45 to 0.68)	
UACR ≤113 mg/mmol (1000 mg/g)	0.9	2.3	0.42 (0.25 to 0.70)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	4.1	7.7	0.52 (0.39 to 0.69)	0.59
UACR >395.5 mg/mmol (3500 mg/g)	16.7	27.7	0.62 (0.42 to 0.90)	
Secondary outcome: CV death or hHF				
Overall	2.2	3.0	0.71 (0.55 to 0.92)	
UACR ≤113 mg/mmol (1000 mg/g)	1.7	2.5	0.70 (0.47 to 1.05)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	2.2	3.2	0.70 (0.47 to 1.04)	0.98
UACR >395.5 mg/mmol (3500 mg/g)	4.8	7.0	0.67 (0.35 to 1.28)	
Secondary outcome: All-cause mortality				
Overall	2.2	3.1	0.69 (0.53 to 0.88)	
UACR ≤113 mg/mmol (1000 mg/g)	1.9	2.9	0.68 (0.47 to 0.98)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	2.0	3.1	0.64 (0.43 to 0.96)	0.83
UACR >395.5 mg/mmol (3500 mg/g)	4.7	5.7	0.83 (0.42 to 1.63)	

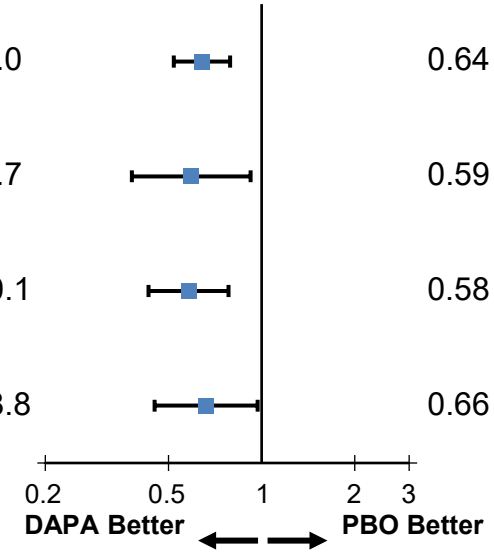


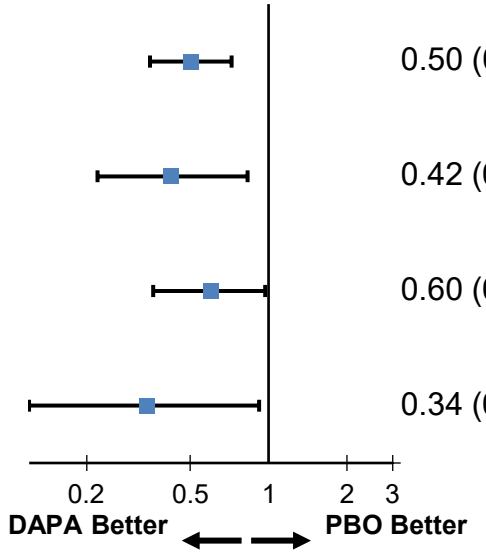
CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; pt-yrs = patient-years; UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

Primary Composite Outcome[a] by Baseline Albuminuria in Patients With and Without T2D

	With T2D				Without T2D			
	Events/ 100 pt-yrs		HR (95% CI)	P-Int	Events/ 100 pt-yrs		HR (95% CI)	P-Int
	DAPA	PBO			DAPA	PBO		
Overall	5.2	8.0	0.64 (0.52 to 0.79)		3.4	6.3	0.50 (0.35 to 0.72)	
UACR ≤113 mg/mmol (1000 mg/g)	2.1	3.7	0.59 (0.38 to 0.92)		1.6	3.8	0.42 (0.22 to 0.83)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	5.9	10.1	0.58 (0.43 to 0.78)	0.93	5.0	7.6	0.60 (0.36 to 0.97)	0.42
UACR >395.5 mg/mmol (3500 mg/g)	19.1	28.8	0.66 (0.45 to 0.97)		16.1	46.6	0.34 (0.12 to 0.92)	





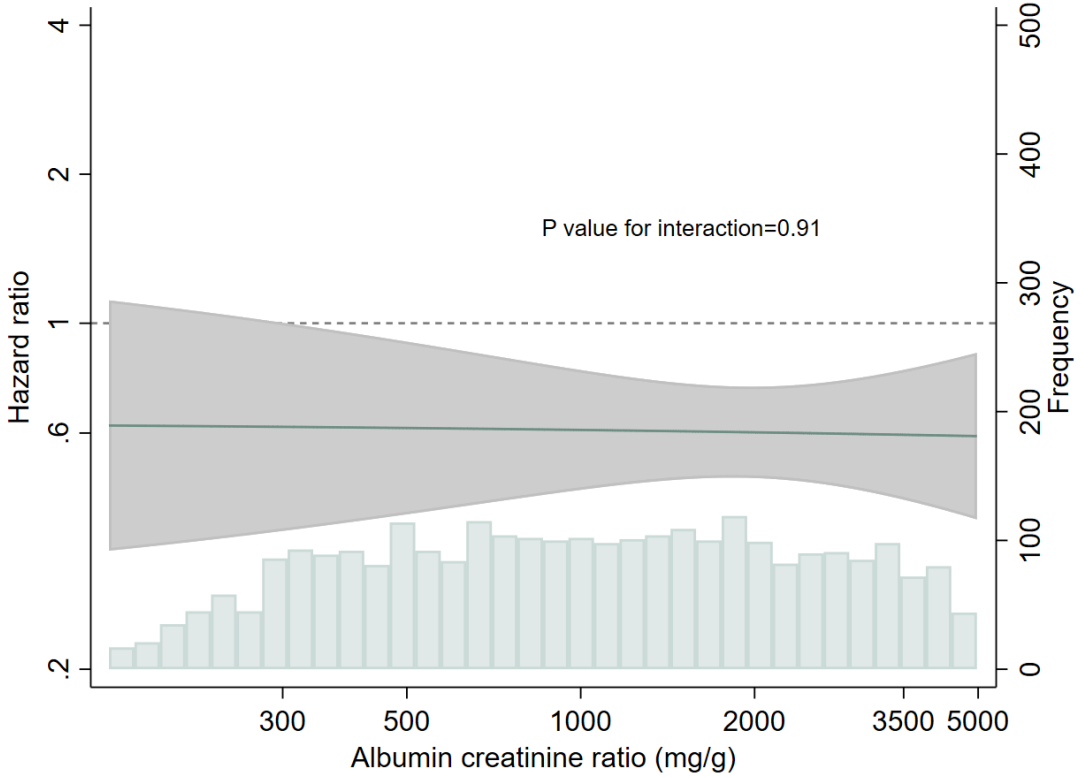
[a]Sustained ≥50% eGFR Decline, ESKD, kidney death, or CV death.

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; PBO = placebo; P-Int = p value for interaction; pt-yrs = patient-years; T2D = type 2 diabetes; UACR = urinary albumin-to-creatine ratio.

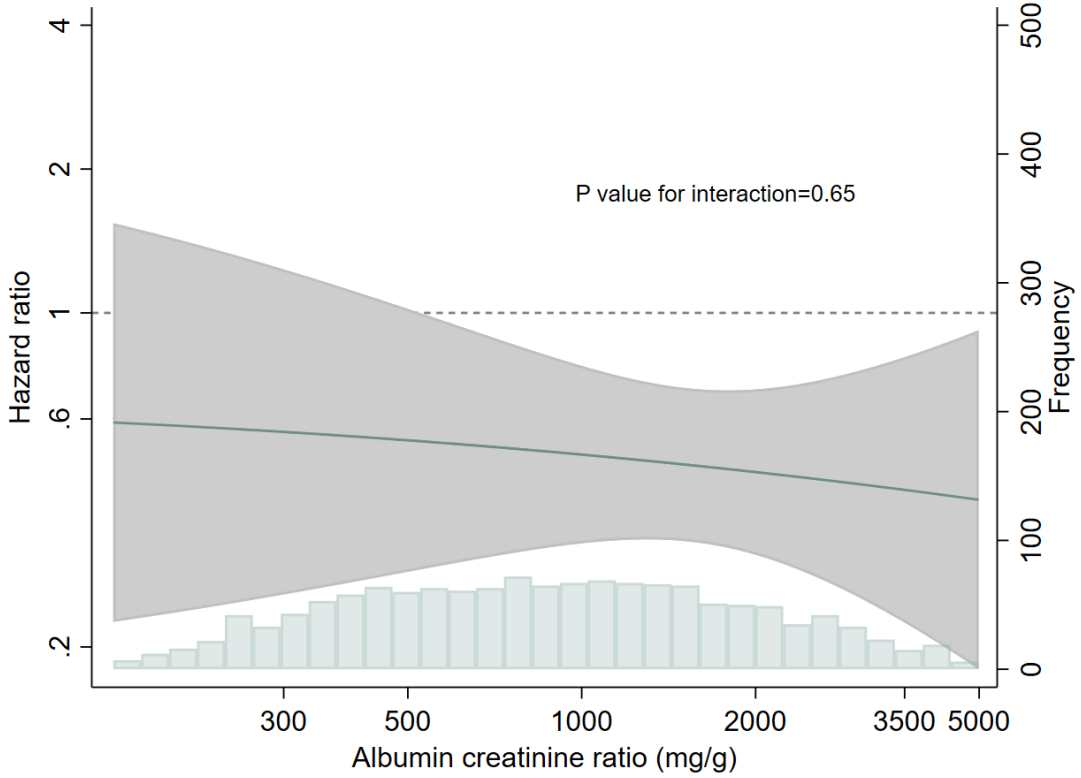
Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

Primary Composite Outcome[a] by Baseline Albuminuria in Patients With and Without T2D

With type 2 diabetes



Without type 2 diabetes



[a]Sustained ≥50% eGFR Decline, ESKD, kidney death, or CV death.

The solid line indicates the hazard ratio for the primary outcome across baseline UACR, the shaded area indicates the 95%CI

The histogram shows the distribution of UACR at baseline.

UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

Adverse Events by Baseline Albuminuria

	Dapagliflozin (%)	Placebo (%)	Odds ratio (95% CI)	P for interaction
Discontinuation due to adverse event				
Overall	5.5	5.7	0.97 (0.74 to 1.26)	
UACR ≤113 mg/mmol (1000 mg/g)	5.0	4.5	1.12 (0.76 to 1.66)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	5.3	6.1	0.87 (0.58 to 1.30)	0.48
UACR >395.5 mg/mmol (3500 mg/g)	9.6	12.8	0.71 (0.35 to 1.46)	
Any serious adverse event[a]				
Overall	29.5	33.9	0.81 (0.72 to 0.93)	
UACR ≤113 mg/mmol (1000 mg/g)	25.8	30.7	0.78 (0.65 to 0.95)	
UACR >113 to ≤395.5 mg/mmol (1000-3500 mg/g)	31.7	35.5	0.85 (0.69 to 1.03)	0.79
UACR >395.5 mg/mmol (3500 mg/g)	42.2	48.6	0.77 (0.49 to 1.22)	

[a]Includes death

UACR = urinary albumin-to-creatine ratio

Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

Summary

- Dapagliflozin consistently reduced the risk of cardiorenal outcomes and all-cause mortality across subgroups of baseline albuminuria
- When stratified by baseline albuminuria, results were consistent in patients with and without T2D
- Adverse events leading to study drug discontinuation or serious adverse events were similar between treatment groups and consistent when stratified by baseline albuminuria

T2D = type 2 diabetes

Waijer SW et al. Presented at Virtual EASD Annual Meeting 2021; September 27-October 1st; Virtual.

DAPA-CKD Exploratory Analysis
Effect on eGFR

In a prespecified analysis from DAPA-CKD, the effect of dapagliflozin versus placebo on eGFR was assessed in patients with CKD, with or without T2D

CKD = chronic kidney disease; T2D = type 2 diabetes.

Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

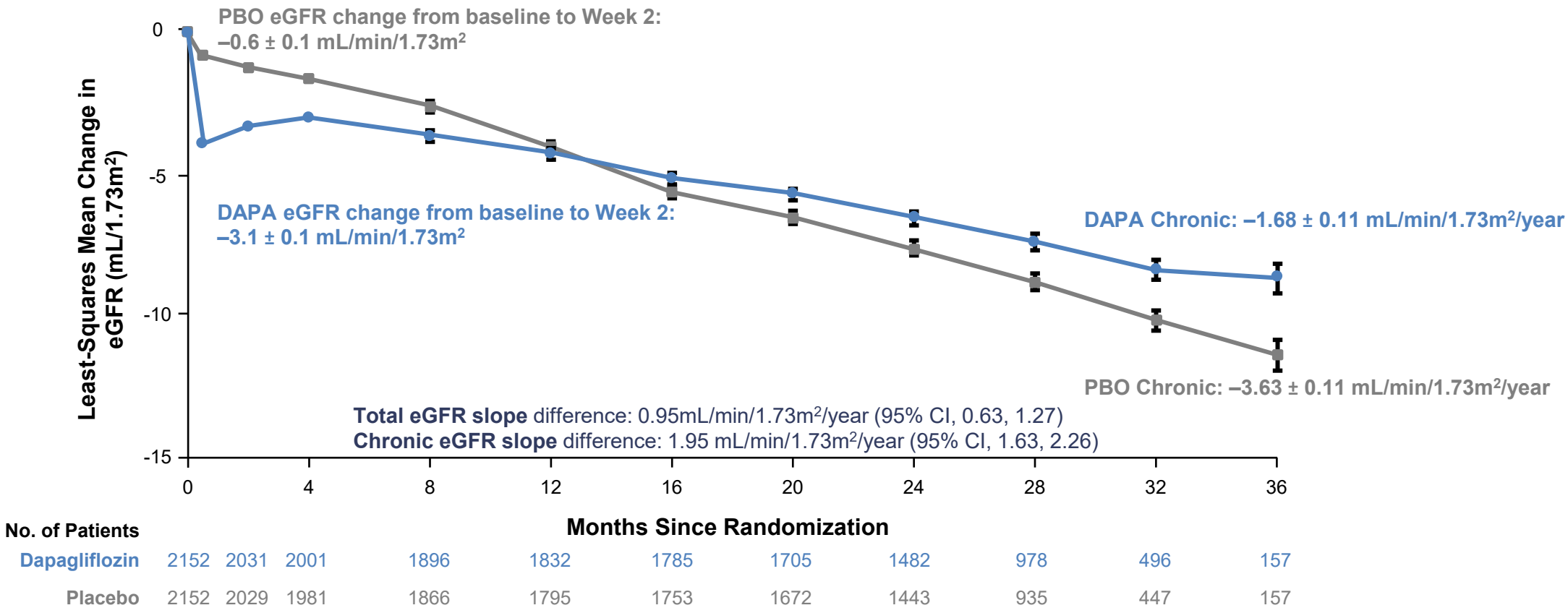
Baseline Characteristics by eGFR Subgroups

Characteristic	eGFR <45 mL/min/1.73m²		eGFR ≥45 mL/min/1.73m²	
	Dapagliflozin n=1272	Placebo N=1250	Dapagliflozin n=880	Placebo n=902
Age, years, mean	62.2	62.1	61.2	61.6
Sex, female, %	34.1	34.2	31.2	31.9
Race, %				
White	52.8	54.1	51.4	54.3
Black/African-American	4.8	4.0	4.9	4.1
Asian	35.5	34.1	33.9	32.4
Other[a]	6.9	7.8	9.9	9.2
Blood pressure, mmHg, mean SBP	137.1	137.3	136.2	137.6
eGFR, mL/min/1.73m², mean	34.7	34.2	55.5	55.1
UACR, mg/mmol, median	120.0	108.3	91.2	102.6
mg/g	1060	958	807	908
HbA1c, %, mean	6.9	6.9	7.3	7.2
Type 2 diabetes, %	64.9	65.1	71.5	70.6
History of CVD, %	38.2	36.4	37.2	37.9

CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; SBP = systolic blood pressure; UACR = urinary albumin-to-creatine ratio.

Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

Change From Baseline in eGFR in the Overall Population[1,2]



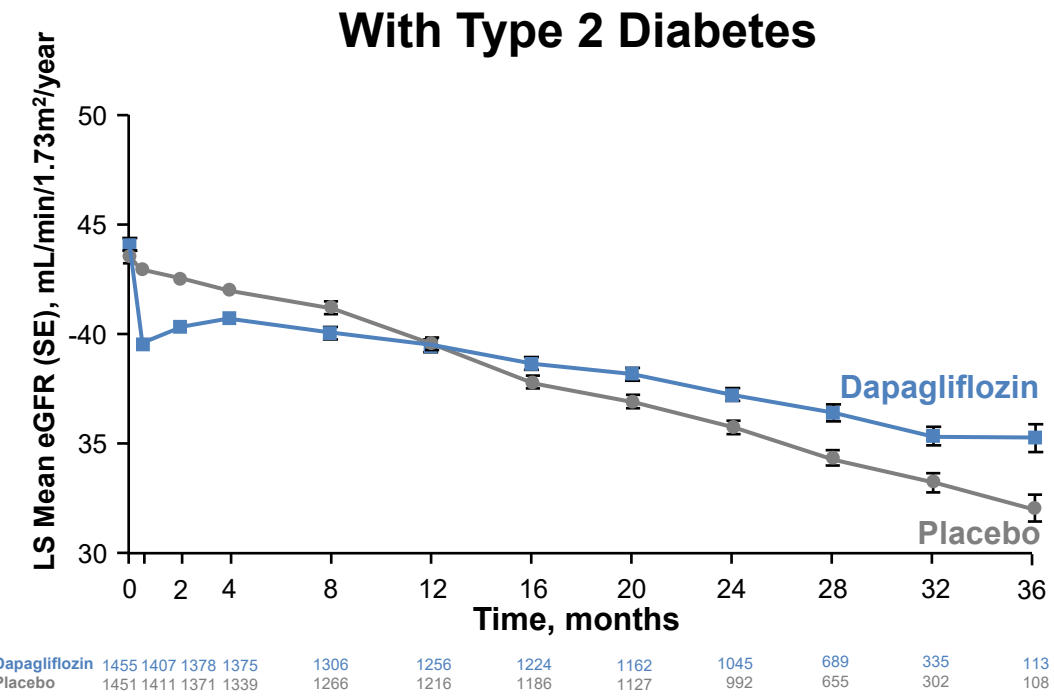
No. of Patients											
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157

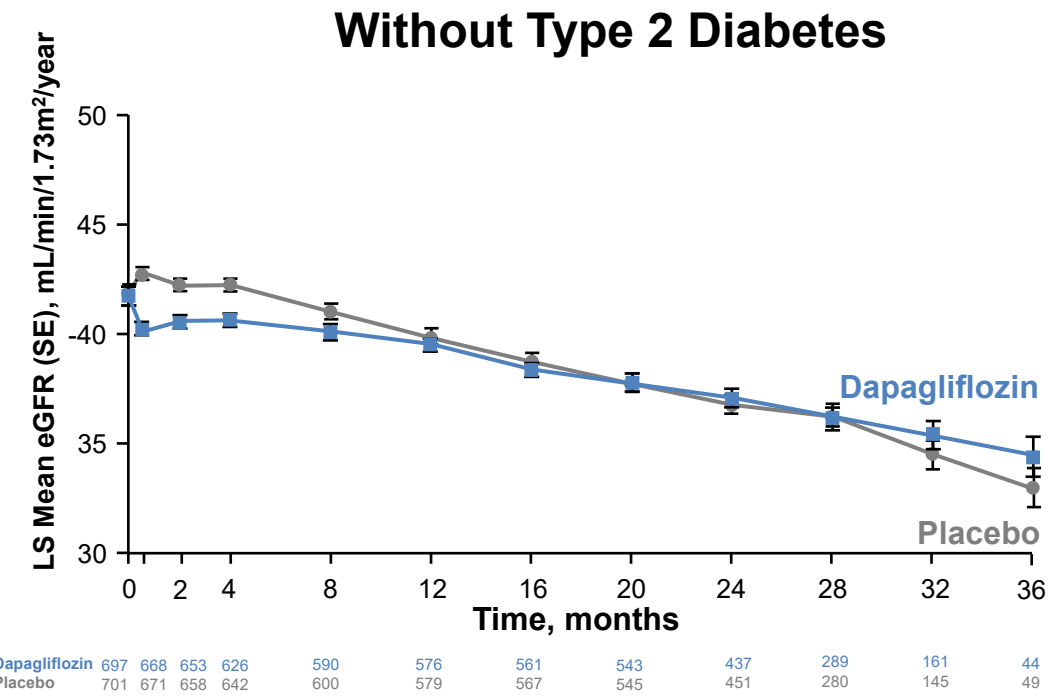
Acute eGFR Decline by Subgroups
Acute eGFR Decline and Safety

BL = baseline; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

Change From Baseline in eGFR by Diabetes Status





eGFR Slope, mean (SE)[a]	DAPA	PBO	Difference
Acute[b], per 2 weeks	–3.2 (0.2)	–0.6 (0.2)	–2.61 (95%CI -3.06, -2.16)
Chronic[c], per year	–1.58 (0.14)	–3.84 (0.14)	2.26 (95%CI 1.88, 2.64)
Total[d], per year	–2.84 (0.14)	–4.01 (0.14)	1.18 (95%CI 0.79, 1.56)

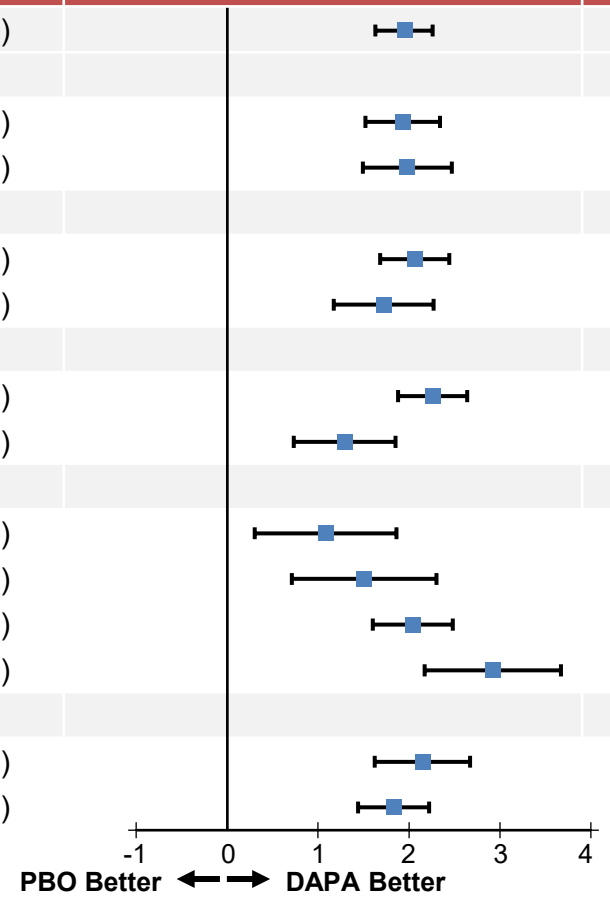
eGFR Slope, mean (SE)[a]	DAPA	PBO	Difference
Acute[b], per 2 weeks	–2.8 (0.2)	–0.8 (0.2)	–2.01 (95%CI -2.66, -1.36)
Chronic[c], per year	–1.90 (0.20)	–3.18 (0.20)	1.29 (95%CI 0.73, 1.85)
Total[d], per year	–2.97 (0.20)	–3.43 (0.20)	0.46 (95%CI –0.10, 1.03)

[a]All values are mL/min/1.73m^2; [b]Acute: change from baseline to two weeks after randomization; [c]Chronic: change from two weeks to end of treatment; [d]Total: change from baseline to end of treatment
CI = confidence interval; eGFR = estimated glomerular filtration rate; SE = standard error.

Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

Chronic eGFR Slope (Week 2 to End of Treatment) by Baseline Subgroups

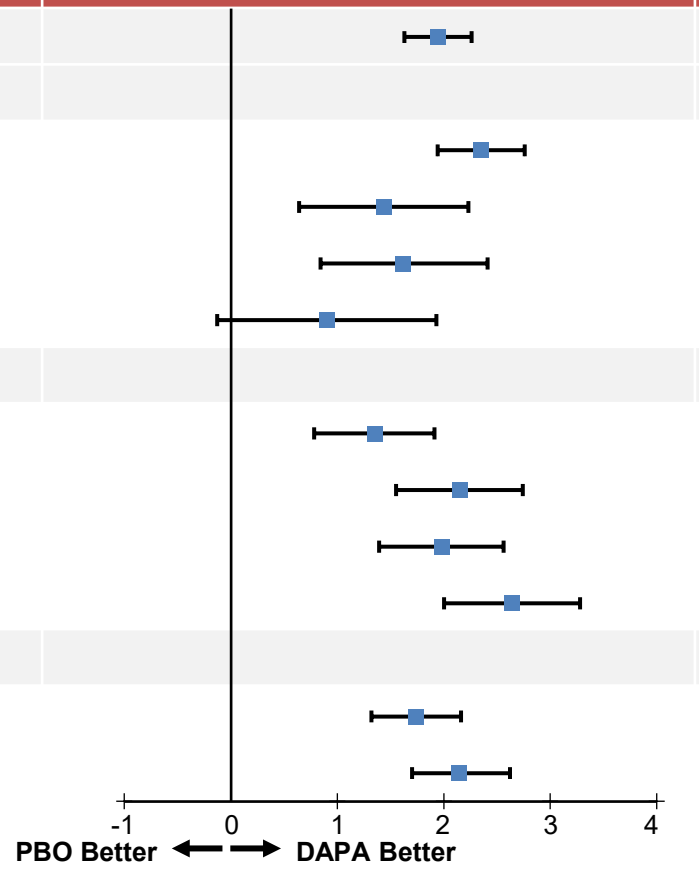
	Chronic eGFR Slope[a]		Difference (95% CI)[b]	P-value for Interaction	% Change
	DAPA	PBO			
Overall	-1.68 (0.11)	-3.63 (0.11)	1.95 (1.63 to 2.26)		53.7
Age, years					
≤65 years	-1.98 (0.15)	-3.91 (0.15)	1.93 (1.52 to 2.34)	0.876	49.4
>65 years	-1.27 (0.17)	-3.24 (0.18)	1.98 (1.49 to 2.47)		60.8
Sex					
Male	-1.66 (0.14)	-3.72 (0.14)	2.06 (1.68 to 2.44)	0.320	55.4
Female	-1.72 (0.20)	-3.45 (0.20)	1.72 (1.17 to 2.27)		50.1
T2D					
Yes	-1.58 (0.14)	-3.84 (0.14)	2.26 (1.88 to 2.64)	0.005	58.9
No	-1.90 (0.20)	-3.18 (0.20)	1.29 (0.73 to 1.85)		40.3
HbA1c					
Normoglycemia	-2.06 (0.28)	-3.14 (0.28)	1.08 (0.30 to 1.86)	0.070	34.4
Pre-diabetes	-1.72 (0.29)	-3.23 (0.29)	1.50 (0.71 to 2.30)		46.7
≤8.5%[c]	-1.46 (0.16)	-3.50 (0.16)	2.04 (1.60 to 2.48)		58.3
>8.5%[c]	-1.94 (0.26)	-4.86 (0.27)	2.92 (2.17 to 3.67)		60.1
Systolic Blood Pressure, mm Hg					
≤130	-1.28 (0.19)	-3.43 (0.19)	2.15 (1.62 to 2.67)	0.343	62.7
>130	-1.91 (0.14)	-3.74 (0.14)	1.83 (1.44 to 2.22)		48.9



[a]Data are mean decline (SE), mL/min/1.73 m^2 per year; [b] Data are mL/min/1.73 m^2 per year; [c]In patients with type 2 diabetes at baseline.
CI = confidence interval; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; PBO = placebo; T2D = type 2 diabetes.
Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

Chronic eGFR Slope (Week 2 to End of Treatment) by Baseline Subgroups, Continued

	Chronic eGFR Slope[a]		Difference (95% CI)[b]	P-value for Interaction	% Change
	DAPA	PBO			
Overall	-1.68 (0.11)	-3.63 (0.11)	1.95 (1.63 to 2.26)		53.7
CKD etiology					
Diabetic nephropathy	-1.62 (0.14)	-3.97 (0.15)	2.35 (1.94 to 2.76)	0.810	59.2
Chronic glomerulonephritis	-2.31 (0.29)	-3,75 (0.28)	1.44 (0.64 to 2.23)		38.4
Hypertensive nephropathy	-1.50 (0.29)	-3.12 (0.27)	1.62 (0.84 to 2.41)		51.9
Other or unknown	-1.32 (0.37)	-2.22 (0.38)	0.90 (-0.13 to 1.93)		40.5
UACR, mg/mmol (mg/g)					
<56.5 (500)	-0.62 (0.20)	-1.97 (0.21)	1.35 (0.78 to 1.91)	0.016	68.5
56.5 to < 113 (500 to <1000)	-0.56 (0.22)	-2.71 (0.21)	2.15 (1.55 to 2.74)		79.3
113 to 226 (1000 to <2000)	-2.00 (0.21)	-3.98 (0.21)	1.98 (1.39 to 2.56)		49.7
≥226 (≥2000)	-3.86 (0.23)	-6.50 (0.24)	2.64 (2.00 to 3.28)		40.6
eGFR, mL/min per 1·73 m²					
<45	-1.48 (0.15)	-3.22 (0.15)	1.74 (1.32 to 2.16)	0.210	54.0
≥45	-1.99 (0.17)	-4.13 (0.17)	2.14 (1.70 to 2.62)		51.8



[a]Data are mean decline (SE), mL/min/1.73 m² per year; [b] Data are mL/min/1.73 m² per year.

CI = confidence interval; CKD = chronic kidney disease; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

Summary

- In this pre-specified analysis of the DAPA-CKD trial, dapagliflozin significantly slowed the rate of eGFR decline in patients with CKD, both with and without T2D
- The effect of dapagliflozin on the rate of eGFR decline over time, compared with placebo, was greater in patients at risk of faster progression, including those with more extensive albuminuria or higher HbA1c

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; T2D = type 2 diabetes.

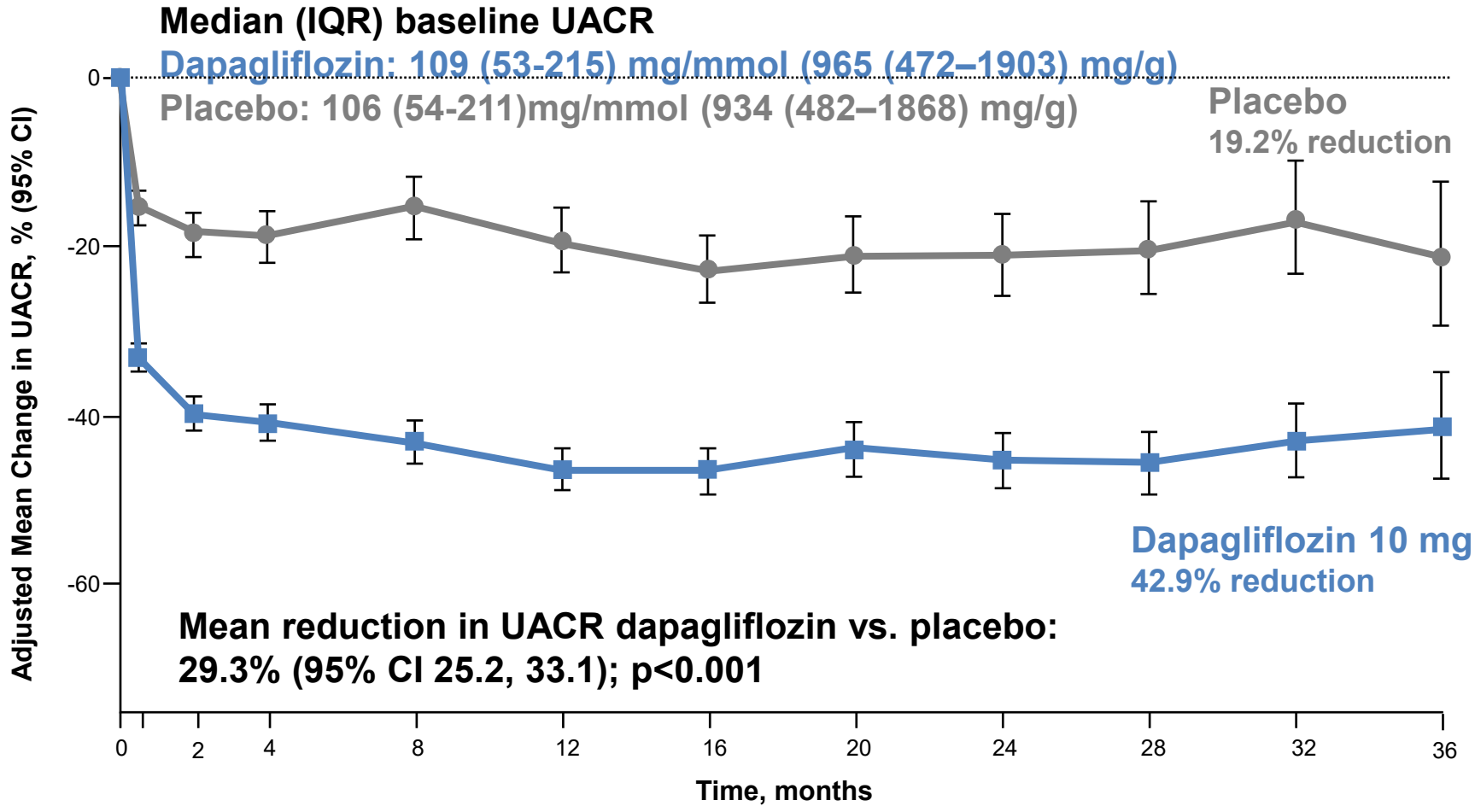
Heerspink HJL et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2021. doi:10.1016/S2213-8587(21)00242-4.

DAPA-CKD Exploratory Analysis
Effect on Albuminuria

In a prespecified analysis from DAPA-CKD, the effect of dapagliflozin versus placebo on albuminuria was assessed in patients with CKD, with or without T2D

CKD = chronic kidney disease; T2D = type 2 diabetes.
Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

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

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

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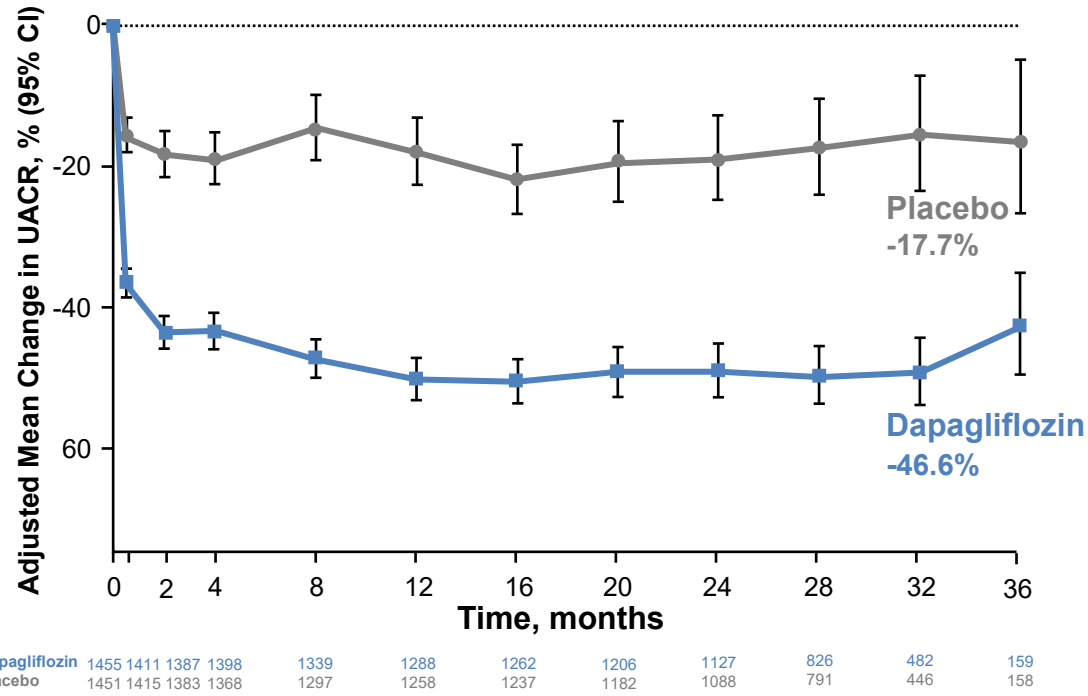
Change in Albuminuria by T2D Status

Patients with T2D

35.1% mean reduction in UACR (dapagliflozin vs. placebo)
(95% CI 30.6, 39.4; p<0.001)

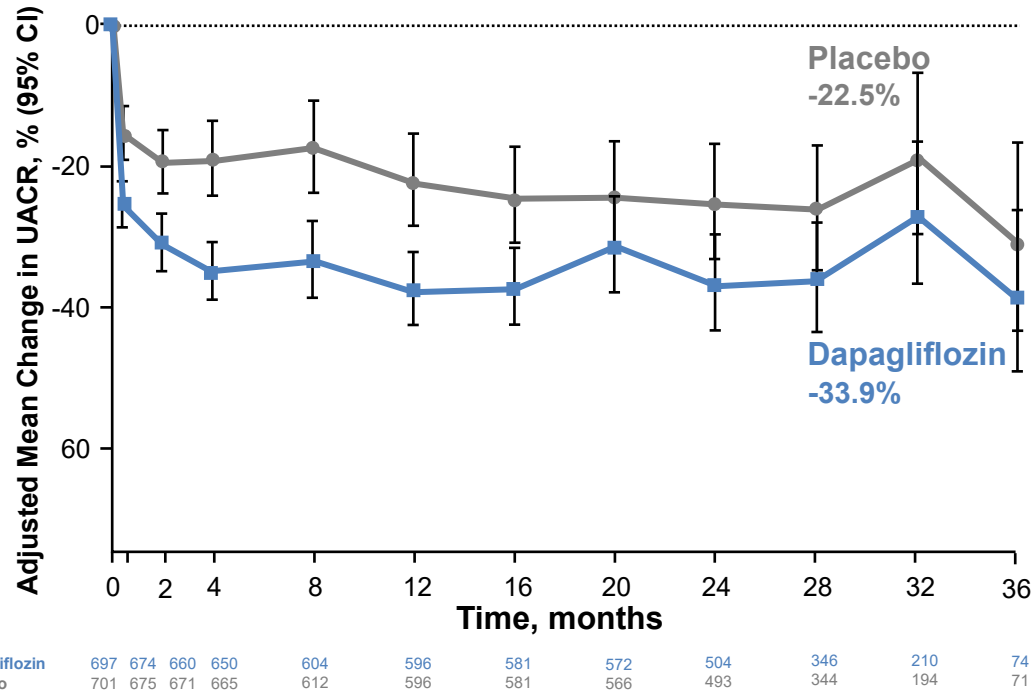


Dapagliflozin	1455	1411	1387	1398	1339	1288	1262	1206	1127	826	482	159
Placebo	1451	1415	1383	1368	1297	1258	1237	1182	1088	791	446	158

Median (IQR) baseline UACR
Dapagliflozin: 116 (54-239) mg/mmol
1025 (473–2111) mg/g
Placebo: 114 (56-228) mg/mmol
1005 (493–2017) mg/g

Patients without T2D

14.8% mean reduction in UACR (dapagliflozin vs. placebo)
(95% CI 5.9, 22.9; p=0.001)



Dapagliflozin	697	674	660	650	604	596	581	572	504	346	210	74
Placebo	701	675	671	665	612	596	581	566	493	344	194	71

Median (IQR) baseline UACR
Dapagliflozin: 98 (53-176) mg/mmol
870 (472–1554) mg/g
Placebo: 95 (52-176) mg/mmol
842 (459–1555) mg/g

CI = confidence interval; IQR = interquartile range; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio
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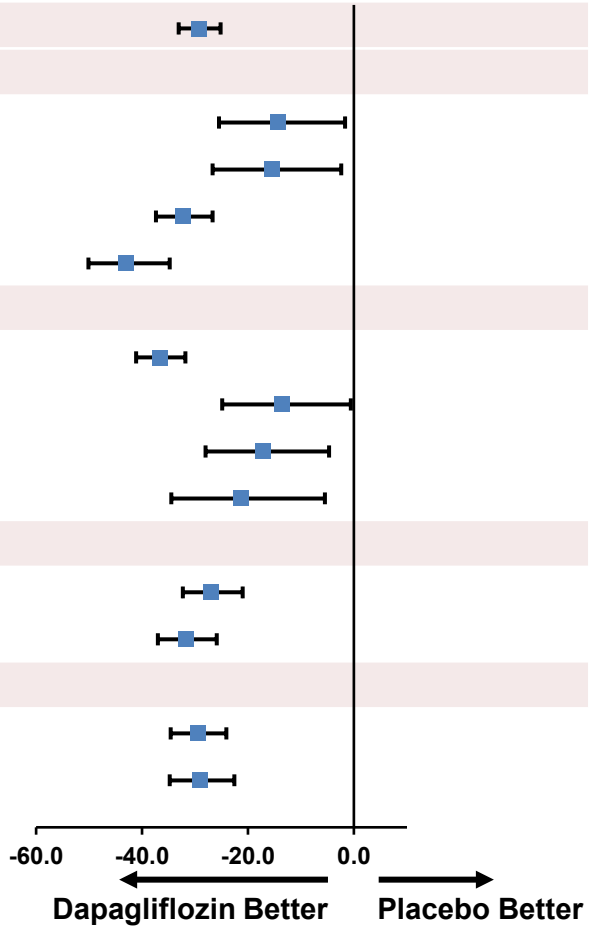
Change in Albuminuria by Baseline Subgroups

	UACR change, % (95% CI)		Effect (Placebo-DAPA) % (95% CI)	P-value for Interaction
	DAPA	Placebo		
Overall	–42.9 (–45.1, –40.6)	–19.2 (–22.4, –15.9)	–29.3 (–33.1, –25.2)	
Baseline glycemic status				
Normoglycemia	–32.5 (–38.8, –25.6)	–21.2 (–28.5, –13.0)	–14.4 (–25.5, –1.7)	<0.001
Pre–diabetes	–35.6 (–41.8, –28.7)	–23.8 (–31.2, –15.7)	–15.4 (–26.7, –2.4)	
Type 2 diabetes and HbA1c <8.5%	–46.5 (–49.4, –43.5)	–21.0 (–25.3, –16.5)	–32.3 (–37.4, –26.7)	
Type 2 diabetes and HbA1c ≥8.5%	–47.1 (–51.8, –41.9)	–7.1 (–15.8, 2.1)	–43.0 (–50.1, –34.8)	
CKD etiology				
Diabetic nephropathy	–47.6 (–50.2, –44.9)	–17.4 (–21.6, –13.0)	–36.6 (–41.1, –31.8)	<0.001
Chronic glomerulonephritides	–24.1 (–31.4, –16.1)	–12.2 (–20.4, –3.1)	–13.6 (–24.9, –0.6)	
Hypertensive nephropathy	–37.0 (–43.1, –30.3)	–24.0 (–31.0, –16.2)	–17.2 (–28.0, –4.7)	
Other/unknown	–47.6 (–53.8, –40.4)	–33.3 (–41.6, –23.9)	–21.3 (–34.5, –5.5)	
Baseline UACR				
≤113 mg/mmol (1000 mg/g)	–36.5 (–39.9, –32.9)	–13.2 (–17.9, –8.3)	–26.9 (–32.3, –21.0)	0.24
>113 mg/mmol (1000 mg/g)	–49.0 (–51.8, –46.0)	–25.4 (–29.6, –20.9)	–31.7 (–37.0, –25.9)	
Baseline eGFR				
<45 mL/min/1.73m^2	–39.3 (–42.4, –36.1)	–13.9 (–18.4, –9.2)	–29.5 (–34.6, –24.1)	0.28
≥45 mL/min/1.73m^2	–47.3 (–50.5, –44.0)	–25.8 (–30.2, –21.2)	–29.0 (–34.8, –22.6)	



CI = confidence interval; CKD = chronic kidney disease; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; UACR = urinary albumin-to-creatinine ratio.

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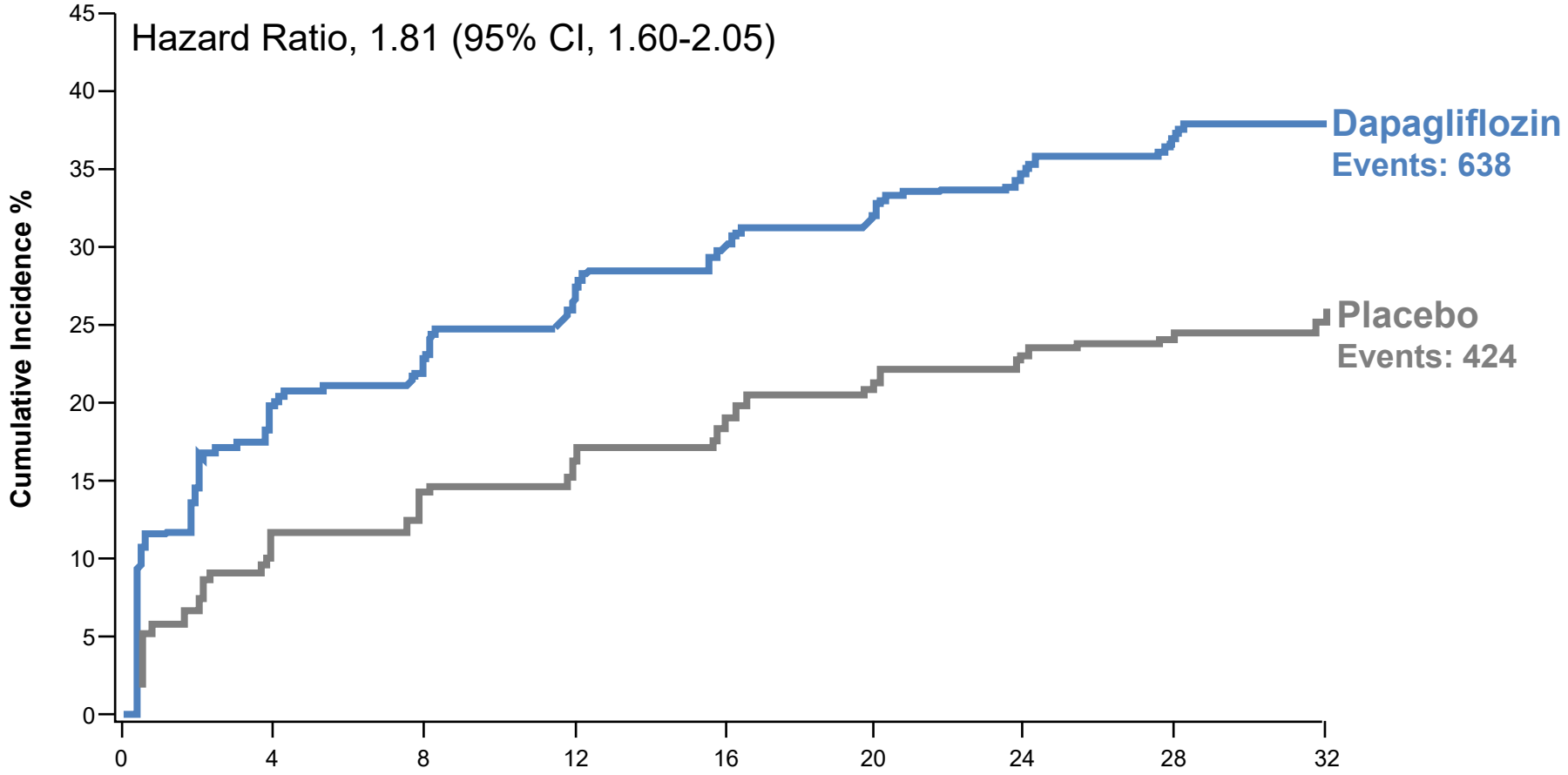
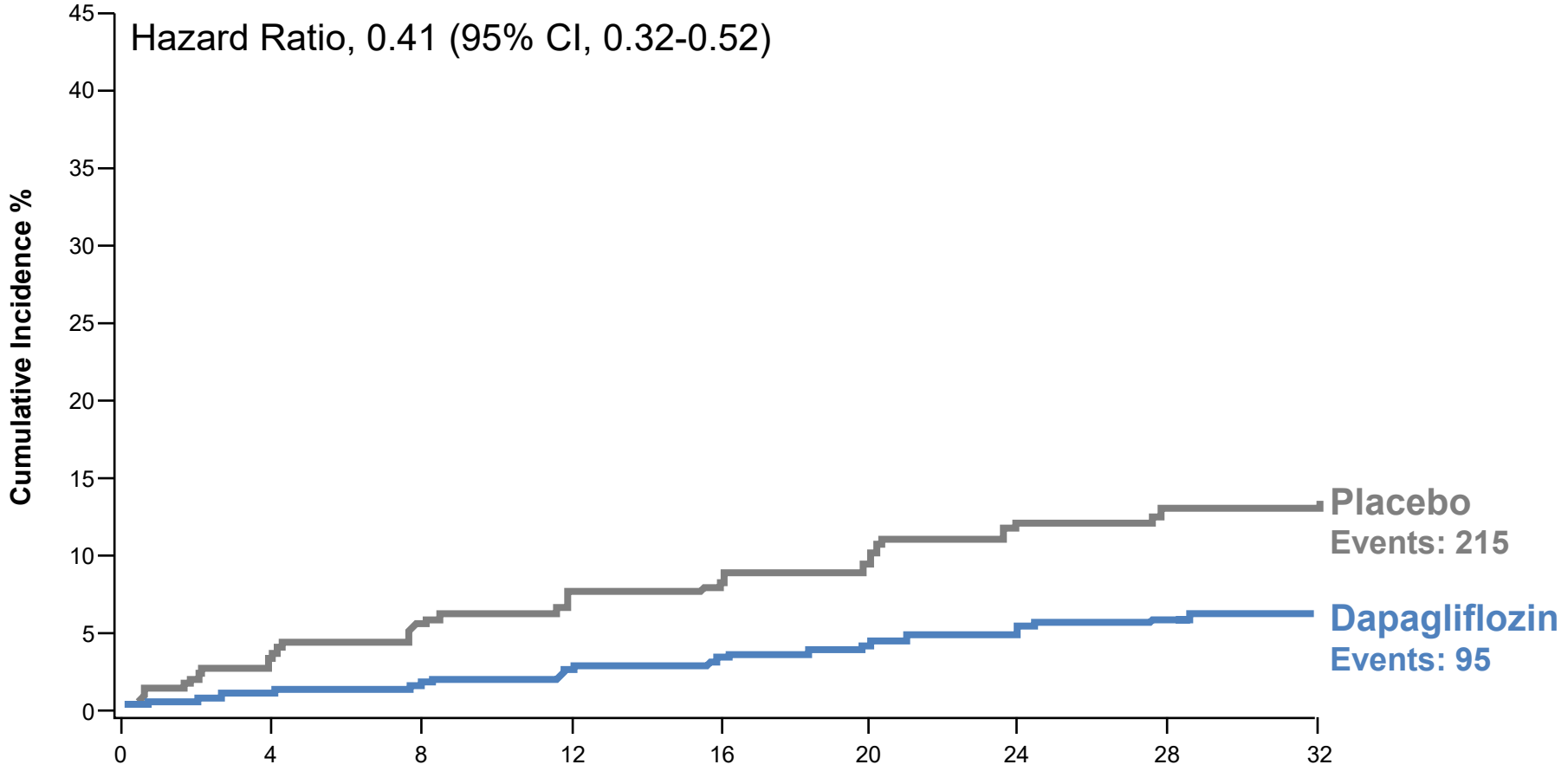
Regression to UACR <33.9 mg/mmol (300 mg/g)



Transition from ≥300 mg/g to <300 mg/g albuminuria in patients with UACR ≥300 mg/g at baseline; a hazard ratio >1 favors dapagliflozin vs. placebo
CI = confidence interval; UACR = urinary albumin-to-creatinine ratio
Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

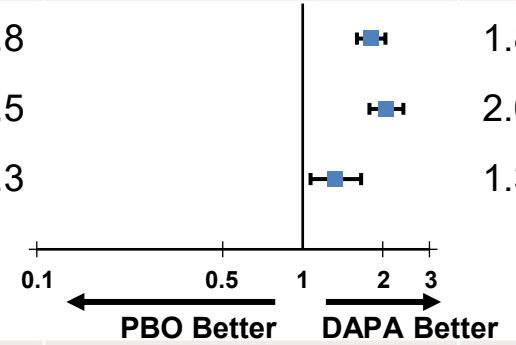
Progression to UACR ≥339 mg/mmol (3000 mg/g)

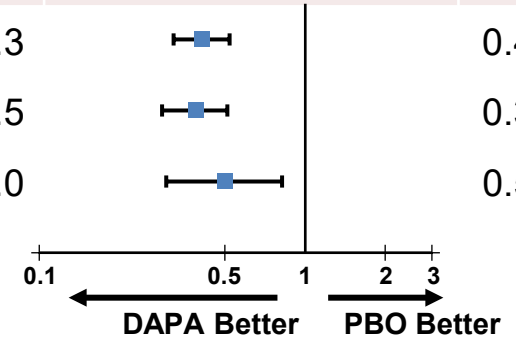


Transition from <3000 mg/g to ≥3000 mg/g albuminuria in patients with UACR <3000 mg/g at baseline; a hazard ratio <1 favors dapagliflozin vs. placebo
CI = confidence interval; UACR = urinary albumin-to-creatinine ratio
Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

Regression and Progression of Albuminuria by Type 2 Diabetes Status at Baseline

	No. of participants/total no.		Events/100 patient-years			Hazard Ratio (95% CI)	P-value for Interaction
	DAPA	PBO	DAPA	PBO			
Regression to UACR <300 mg/g[a]							
Overall	638/1913	424/1947	33.4	21.8		1.81 (1.60, 2.05)	
With type 2 diabetes	464/1288	282/1310	36.0	21.5		2.06 (1.78, 2.39)	0.001
Without type 2 diabetes	174/625	142/637	27.8	22.3		1.33 (1.07, 1.66)	
Progression to UACR ≥3000 mg/g[b]							
Overall	95/1909	215/1911	5.0	11.3		0.41 (0.32, 0.52)	
With type 2 diabetes	71/1251	169/1251	5.7	13.5		0.39 (0.29, 0.51)	0.40
Without type 2 diabetes	24/658	46/660	3.6	7.0		0.50 (0.30, 0.82)	





[a]Transition from ≥300 mg/g to <300 mg/g in patients with UACR ≥300 mg/g at baseline; a hazard ratio >1 favours dapagliflozin vs. placebo; [b]Transition from <3000 mg/g to ≥3000 mg/g albuminuria in patients with UACR <3000 mg/g at baseline; a hazard ratio <1 favours dapagliflozin vs. placebo

CI = confidence interval; DAPA = dapaglifozin; PBO = placebo; UACR = urinary albumin-to-creatinine ratio.

Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

Summary

- In this pre-specified exploratory analysis of the DAPA-CKD trial, dapagliflozin significantly reduced albuminuria in patients with CKD, both with and without T2D

CKD = chronic kidney disease; CV = cardiovascular; egFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

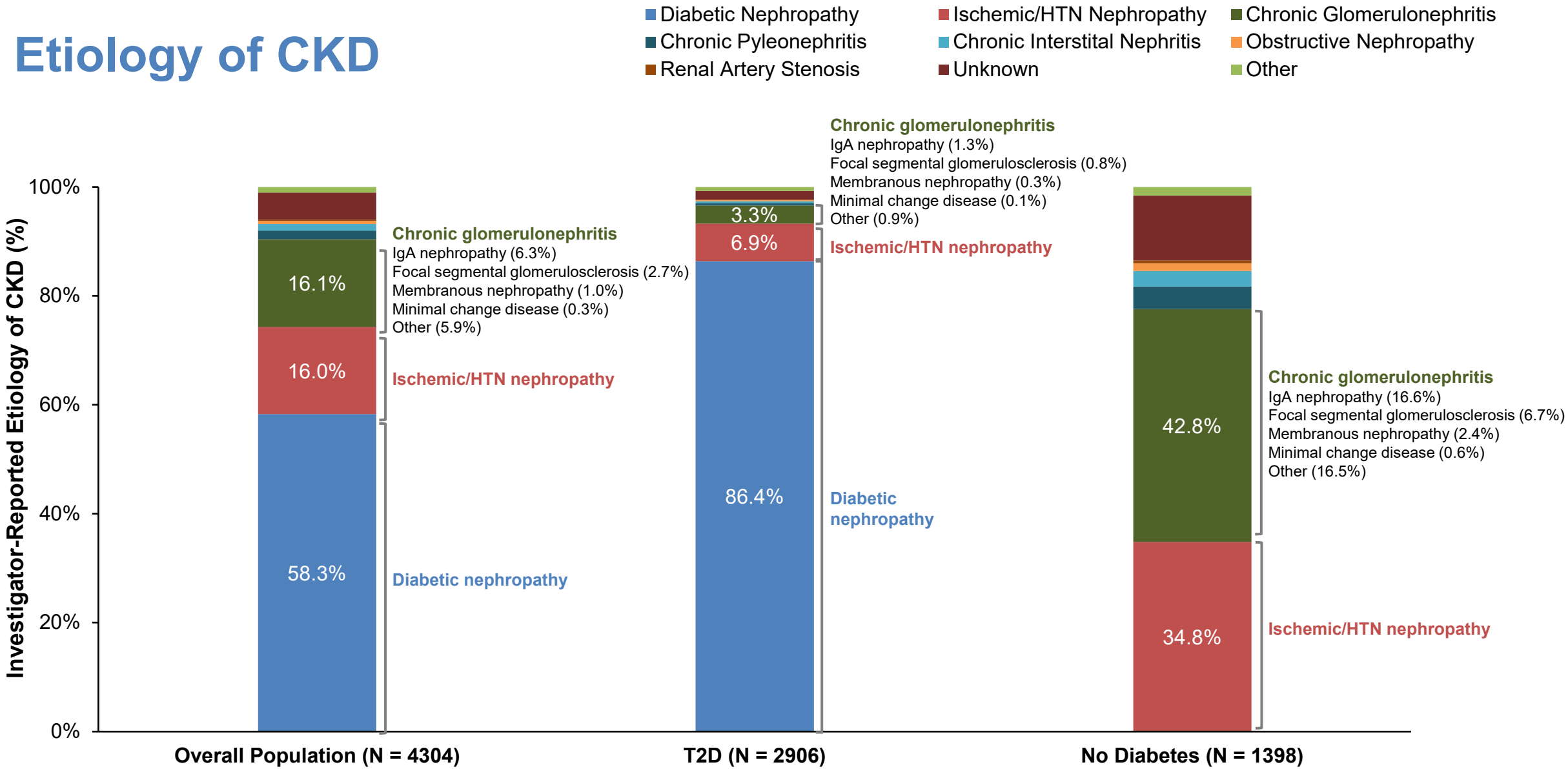
DAPA CKD: In Context

Key Renal Outcome Trials

	SGLT-2i			MRA
	DAPA-CKD[1,2] N = 4304	**CREDENCE[3]** N = 4401	**EMPA-KIDNEY[4]** N ~ 6000	**FIDELIO-DKD[5,6]** N = 5734
Status	**Completed**	**Completed**	**Ongoing** Est. Completion Date June 2022	**Completed**
Intervention	Dapagliflozin vs Placebo ≥4 weeks stable on ACEi or ARB	Canagliflozin vs Placebo ≥4 weeks stable on ACEi or ARB	Empagliflozin vs Placebo On ACEi or ARB	Finerenone vs Placebo ≥4 weeks on ACEi or ARB
Patient Population	• T2D and non-DM • eGFR ≥25 to ≤75 mL/min/1.73m^2 • UACR ≥22.6 to ≤565.6 mg/mmol (≥200 to ≤5000 mg/g)	• T2D • eGFR ≥30 to <90 mL/min/1.73m^2 • UACR >33.9 to ≤565.6 mg/mmol (>300 to ≤5000 mg/g)	• T2D and non-DM • eGFR ≥20 to <45 mL/min/1.73m^2 **or** ≥45 to <90 mL/min/1.73m^2 and UACR ≥22.6 mg/mmol (≥200 mg/g)	• T2D • eGFR ≥25 to <60 mL/min/1.73m^2 and UACR ≥ 3.4 to <33.9 mg/mmol (≥ 30 to <300 mg/g) and diabetic retinopathy **or** eGFR ≥25 to <75 mL/min/1.73m^2 and UACR ≥33.9 mg/mmol (≥300 mg/g)
Primary Endpoint	**Composite** • ≥50% sustained eGFR decline • ESKD • Renal or CV death	**Composite** • Doubling of serum creatinine • ESKD • Renal or CV death	**Composite** • Kidney disease progression • CV death	**Composite** • Kidney failure • ≥40% sustained eGFR decline • Renal death
Secondary Endpoints	• Renal composite • CV death or hHF • All-cause death	• CV death or hHF • CV death, MI, or stroke • hHF • Renal composite • CV death • All-cause death • Composite of CV death, MI, stroke, hHF or hospitalization for UA	• CV death or hHF • All-cause hospitalizations • All-cause death • Kidney disease progression • CV death • CV death or ESKD	• Stroke or hHF • All-cause death • All-cause hospitalizations • ≥57% sustained eGFR decline, kidney failure or renal death • UACR change from baseline

1. Study NCT03036150. ClinicalTrials.gov website. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282. 3. Perkovic V et al. *N Engl J Med*. 2019;380:2295-2306.
4. Study NCT03594110. ClinicalTrials.gov website. 5. Study NCT02540993. ClinicalTrials.gov website. 6. Bakris GL et al. *Am J Nephrol*. 2019;50:333-344.

Etiology of CKD

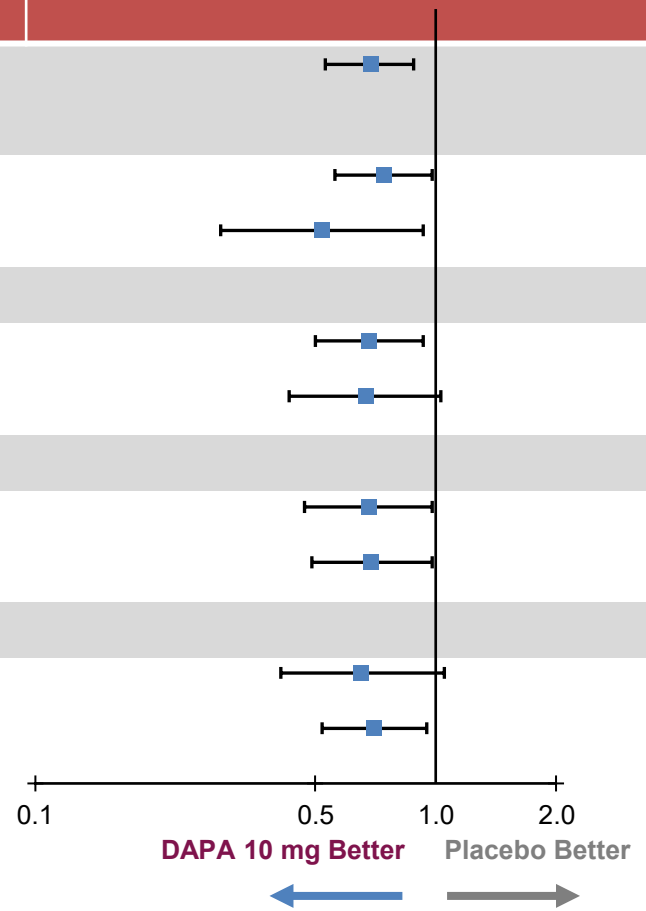


HTN = hypertensive; IgA = immunoglobulin A; T2D = type 2 diabetes.

Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Secondary Outcome – All-cause Mortality: Prespecified Subgroups Analyses[1]

	No. of Patients/Total No.		Events per 100 Patient-years			
	DAPA	Placebo	DAPA	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
Overall	101/2152	146/2152	2.2	3.2	0.69 (0.53, 0.88)	
Type 2 Diabetes						
Yes	84/1455	113/1451	2.6	3.5	0.74 (0.56, 0.98)	0.250
No	17/697	33/701	1.2	2.3	0.52 (0.29, 0.93)	
eGFR						
<45 mL/min/1.73m^2	67/1272	94/1250	2.5	3.6	0.68 (0.50, 0.93)	0.963
≥45 mL/min/1.73m^2	34/880	52/902	1.7	2.6	0.67 (0.43, 1.03)	
Urinary Albumin-to-creatinine Ratio						
≤1000	46/1104	70/1121	1.9	2.7	0.68 (0.47, 0.98)	0.915
>1000	55/1048	76/1031	2.4	3.5	0.69 (0.49, 0.98)	
Systolic Blood Pressure						
≤130	29/793	42/749	1.7	2.7	0.65 (0.41, 1.05)	0.825
>130	72/1359	104/1403	2.4	3.4	0.70 (0.52, 0.95)	

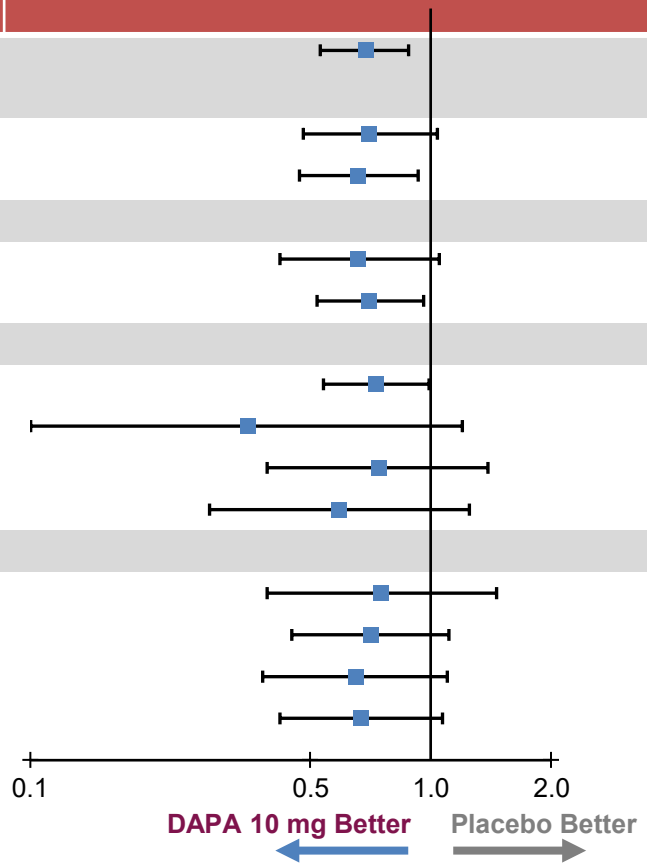


DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate.

[1]Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

Secondary Outcome – All-cause Mortality: Prespecified Subgroups Analyses[1]

	No. of Patients/Total No.		Events per 100 Patient-years			
	DAPA	Placebo	DAPA	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
Overall	101/2152	146/2152	2.2	3.2	0.69 (0.53, 0.88)	
Age						
≤65 years	44/1247	63/1239	1.6	2.4	0.70 (0.48, 1.04)	0.833
>65 years	57/905	83/913	2.8	4.2	0.66 (0.47, 0.93)	
Sex						
Female	31/709	45/716	2.0	2.9	0.66 (0.42, 1.05)	0.821
Male	70/1443	101/1436	2.3	3.3	0.70 (0.52, 0.96)	
Race						
White	69/1124	97/1166	2.7	3.6	0.73 (0.54, 0.99)	0.701
Black	4/104	8/87	1.6	4.1	0.35 (0.10, 1.20)	
Asian	17/749	22/718	1.2	1.6	0.74 (0.39, 1.39)	
Other	11/175	19/181	2.7	4.6	0.59 (0.28, 1.25)	
Geographic Region						
Asia	16/692	20/654	1.2	1.7	0.75 (0.39, 1.46)	0.988
Europe	32/610	46/623	2.3	3.2	0.71 (0.45, 1.11)	
North America	23/401	35/412	2.5	3.7	0.65 (0.38, 1.10)	
Latin America	30/449	45/463	2.9	4.2	0.67 (0.42, 1.07)	



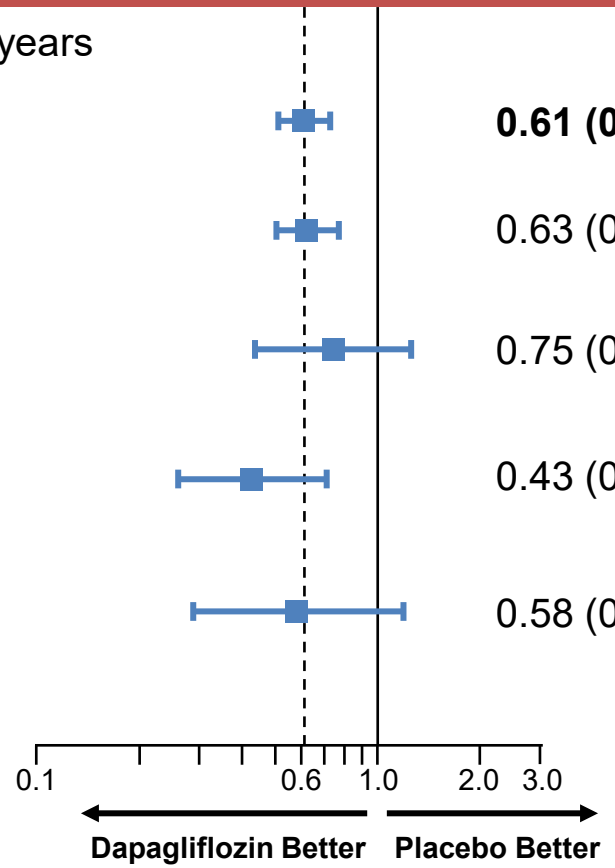
DAPA = dapagliflozin; No = number;

[1]Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

Primary Outcome According to Underlying Cause of Kidney Disease

Composite outcome of sustained ≥50% eGFR decline, ESKD, or renal or cardiovascular death

Primary Outcome	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
	No. of participants/total no.		Events/100 patient-years			
Overall	**197/2152**	**312/2152**	**4.6**	**7.5**	**0.61 (0.51, 0.72)**	
Diabetic nephropathy	139/1271	207/1239	5.4	8.5	0.63 (0.51, 0.78)	0.53
Ischemic/hypertensive nephropathy	24/324	35/363	3.8	4.9	0.75 (0.44, 1.26)	
Glomerulonephritides	22/343	49/352	3.4	7.5	0.43 (0.26, 0.71)	
Other/unknown	12/214	21/198	2.9	5.5	0.58 (0.29, 1.19)	



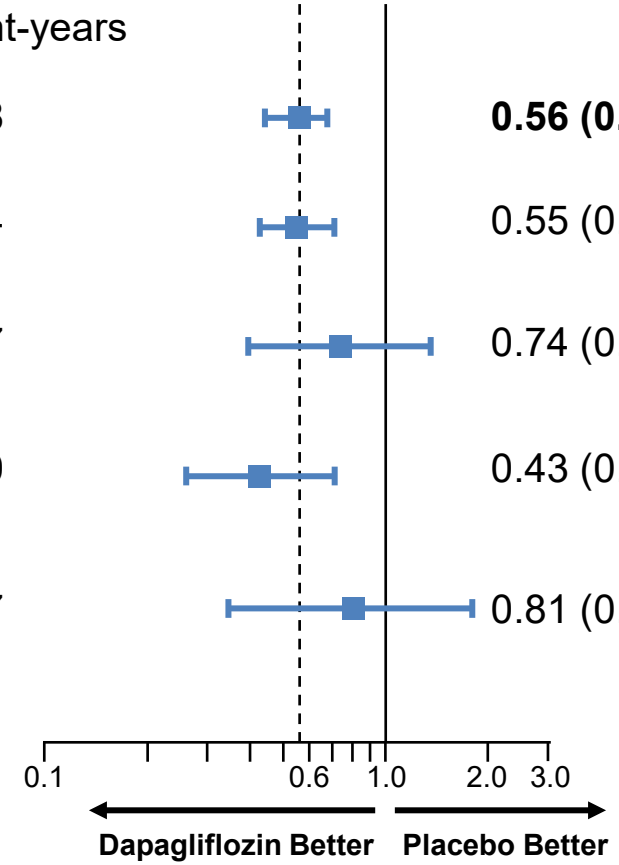
eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease.

Wheeler DC. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

Secondary Outcome: Renal-specific Outcome According to Underlying Cause of Kidney Disease

Composite outcome of sustained ≥50% eGFR decline, ESKD or renal death

Renal-specific outcome	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
	No. of participants/total no.		Events/100 patient-years			
Overall	**142/2152**	**243/2152**	**3.3**	**5.8**	**0.56 (0.45, 0.68)**	
Diabetic nephropathy	93/1271	157/1239	3.6	6.4	0.55 (0.43, 0.71)	0.67
Ischemic/hypertensive nephropathy	18/324	26/363	2.8	3.7	0.74 (0.40, 1.36)	
Glomerulonephritides	21/343	46/352	3.3	7.0	0.43 (0.26, 0.72)	
Other/unknown	10/214	14/198	2.5	3.7	0.81 (0.35, 1.83)	

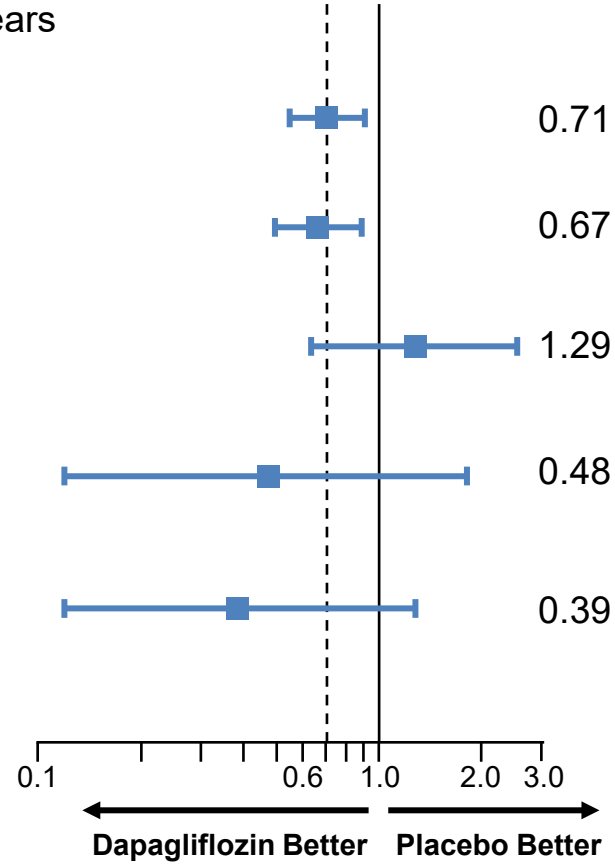


eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease.

Wheeler DC. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

Secondary Outcome: Cardiovascular Death or Hospitalization for Heart Failure According to Underlying Cause of Kidney Disease

CV Death or Heart Failure Hospitalization	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
	No. of participants/total no.		Events/100 patient-years			
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	
Diabetic nephropathy	76/1271	107/1239	2.7	4.0	0.67 (0.50, 0.90)	0.24
Ischemic/hypertensive nephropathy	17/324	15/363	2.5	2.0	1.29 (0.64, 2.60)	
Glomerulonephritides	3/343	7/352	0.4	1.0	0.48 (0.12, 1.84)	
Other/unknown	4/214	9/198	0.9	2.2	0.39 (0.12, 1.28)	



CV = cardiovascular

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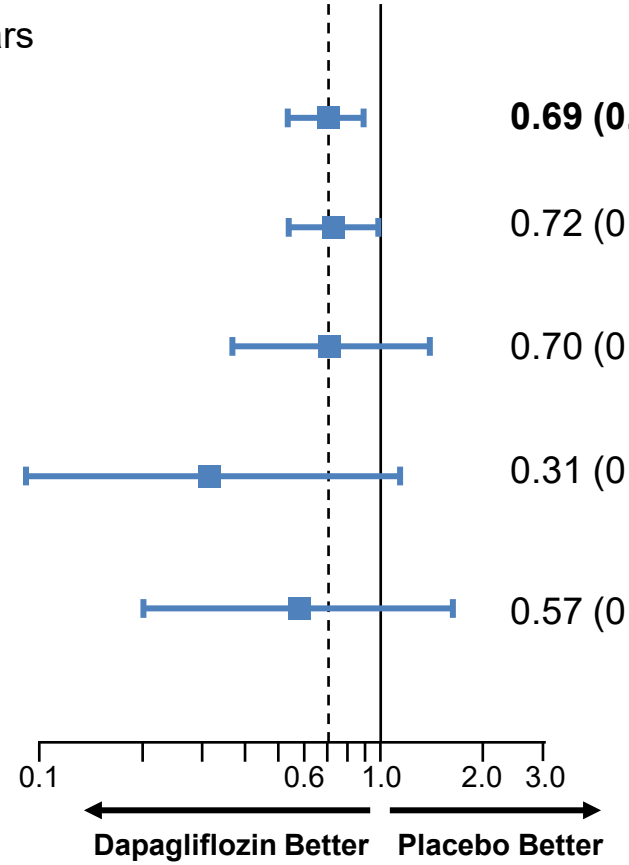
Secondary Outcome: All-cause Mortality According to Underlying Cause of Kidney Disease

All-cause mortality	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
	No. of participants/total no.		Events/100 patient-years			
Overall	**101/2152**	**146/2152**	**2.2**	**3.2**	**0.69 (0.53, 0.88)**	
Diabetic nephropathy	78/1271	104/1239	2.7	3.8	0.72 (0.54, 0.97)	0.55
Ischemic/hypertensive nephropathy	14/324	22/363	2.0	2.8	0.70 (0.36, 1.37)	
Glomerulonephritides	3/343	11/352	0.4	1.5	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	1.3	2.2	0.57 (0.20, 1.61)	



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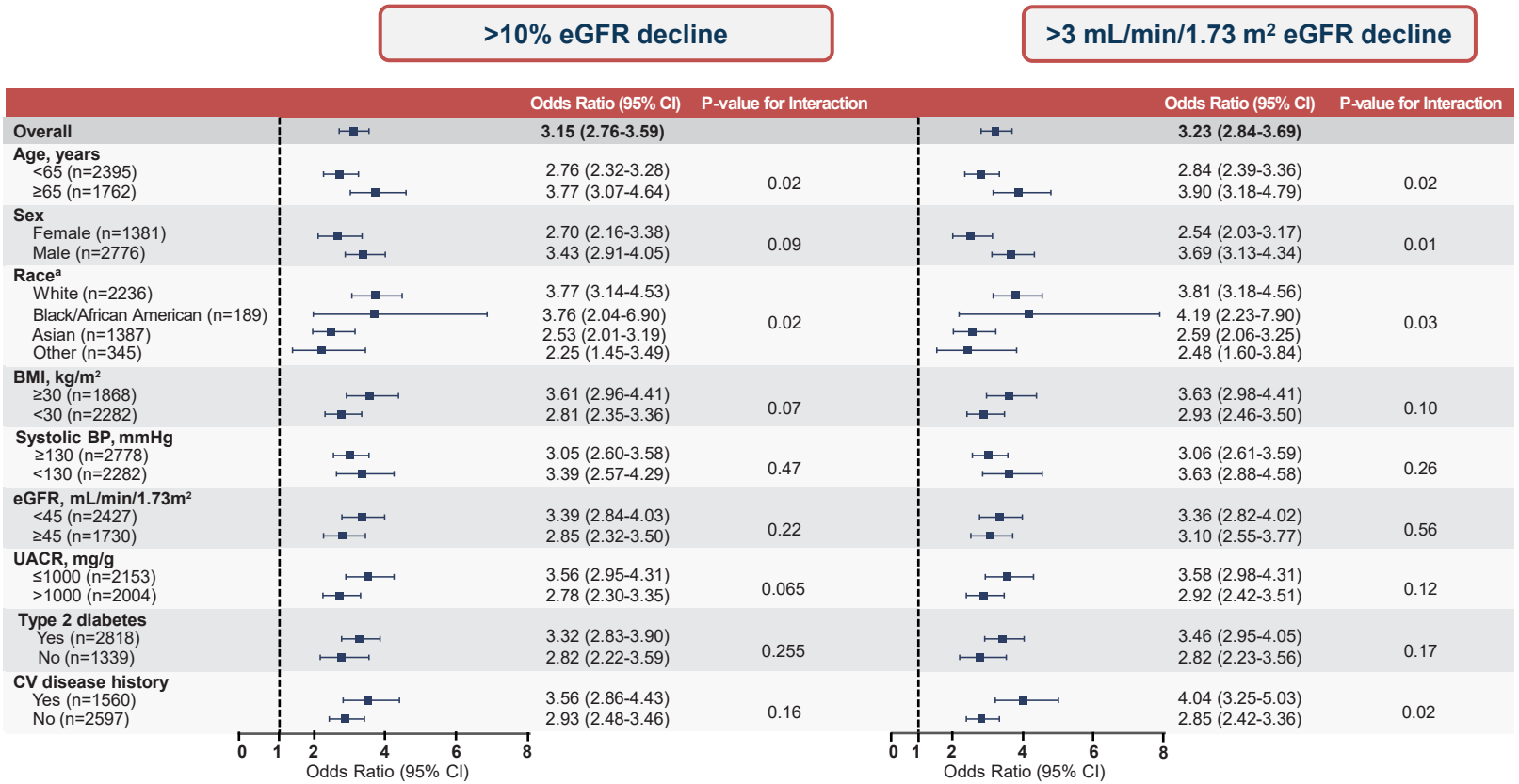
Acute eGFR Decline Across Subgroups

Effect of Dapagliflozin Versus Placebo on Acute eGFR Decline



[a]Reported by the investigator.

BMI = body mass index; BP = blood pressure; CV = cardiovascular; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

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Safety Outcomes by Acute eGFR Decline

Outcome, n (%)	Dapagliflozin (N=2075)			Placebo (N=2082)		
By percentage decline	**>10% (n=1026)**	**0–10% (n=714)**	**<0% (n=335)**	**>10% (n=494)**	**0–10% (n=787)**	**<0% (n=801)**
Discontinuation due to AE	58 (5.6)	38 (5.3)	19 (5.7)	36 (7.3)	39 (5.0)	43 (5.4)
Any serious AE[a]	317 (30.9)	199 (27.9)	102 (30.4)	176 (35.6)	273 (34.7)	262 (32.7)
Kidney-related event[b]	87 (8.5)	39 (5.5)	26 (7.8)	55 (11.1)	72 (9.1)	56 (7.0)
Volume depletion event[b]	71 (6.9)	30 (4.2)	21 (6.3)	20 (4.0)	36 (4.6)	33 (4.1)
By absolute decline, mL/min/1.73 m²	**>3 (n=1137)**	**0–3 (n=603)**	**<0 (n=335)**	**>3 (n=576)**	**0–3 (n=705)**	**<0 (n=801)**
Discontinuation due to AE	58 (5.1)	38 (6.3)	19 (5.7)	34 (5.9)	41 (5.8)	43 (5.4)
Any serious AE[a]	335 (29.5)	181 (30.0)	102 (30.4)	201 (34.9)	248 (35.2)	262 (32.7)
Kidney-related event[b]	88 (7.7)	38 (6.3)	26 (7.8)	57 (9.9)	70 (9.9)	56 (7.0)
Volume depletion event[b]	74 (6.5)	27 (4.5)	21 (6.3)	24 (4.2)	32 (4.5)	33 (4.1)

Acute eGFR Decline With Dapagliflozin Was Not Associated With Increased Risk of AEs, Regardless of Magnitude of Decline

[a]Includes death; [b]Based on predefined list of preferred terms.

AE = adverse event; eGFR = estimated glomerular filtration rate.

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