Global Medical Affairs Cover Sheet

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

Veeva Vault MedComms Document Number: ML-1026-ALL-0225

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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 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, as well as a trend towards improved 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.

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 ≥200 to ≤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. *N Engl J Med*. 2020; 383:1436-1446.

Countries Participating in DAPA-CKD[1,2]

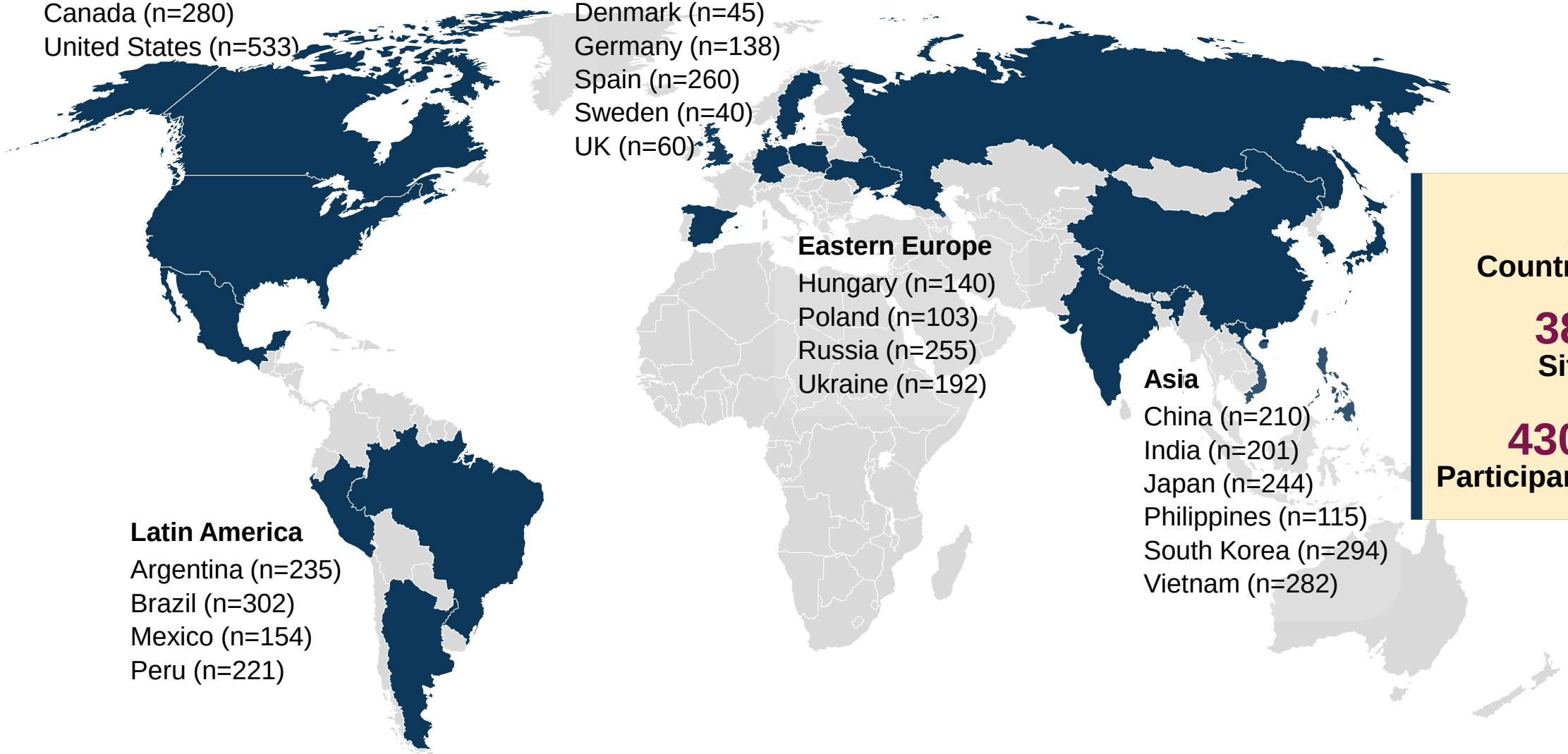
North America
Canada (n=280)
United States (n=533)

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.

Demographics and 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/g, median	965	934
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. *N Engl J Med*. 2020; 383:1436-1446.

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

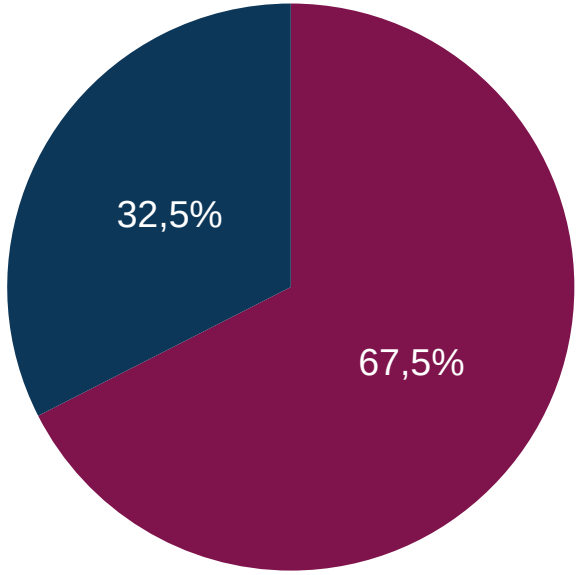
Medical History and BL Medications by Diabetes Status

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

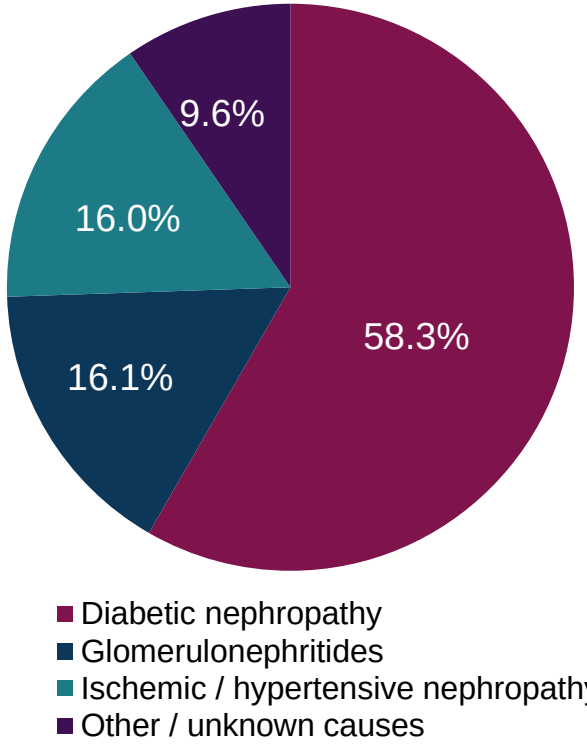
Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

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

Diabetes Status



Investigator-reported Cause of Kidney Disease



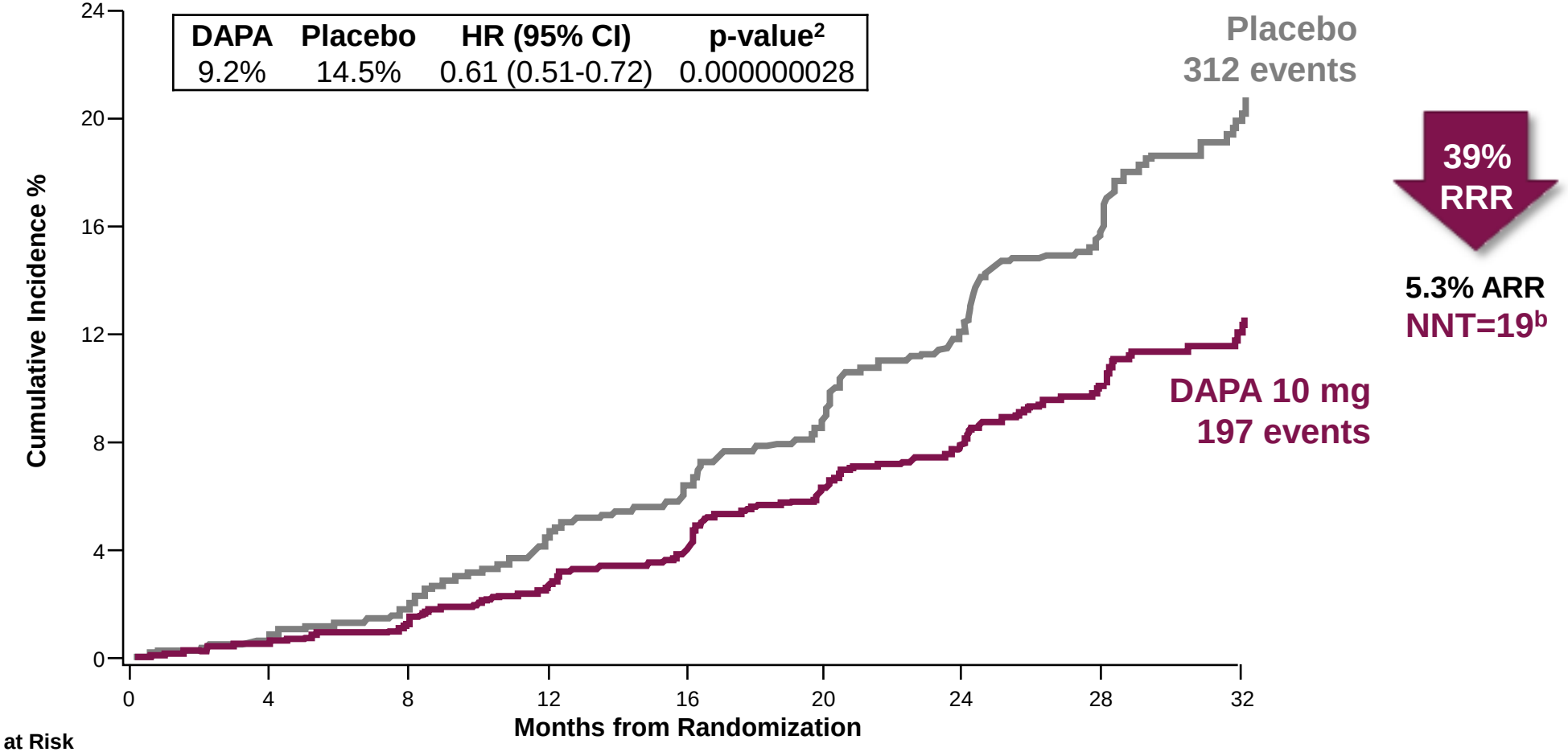
CKD Etiologies

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]

DAPA	Placebo	HR (95% CI)	p-value[2]
9.2%	14.5%	0.61 (0.51-0.72)	0.000000028



N at Risk									
DAPA 10 mg	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

[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.

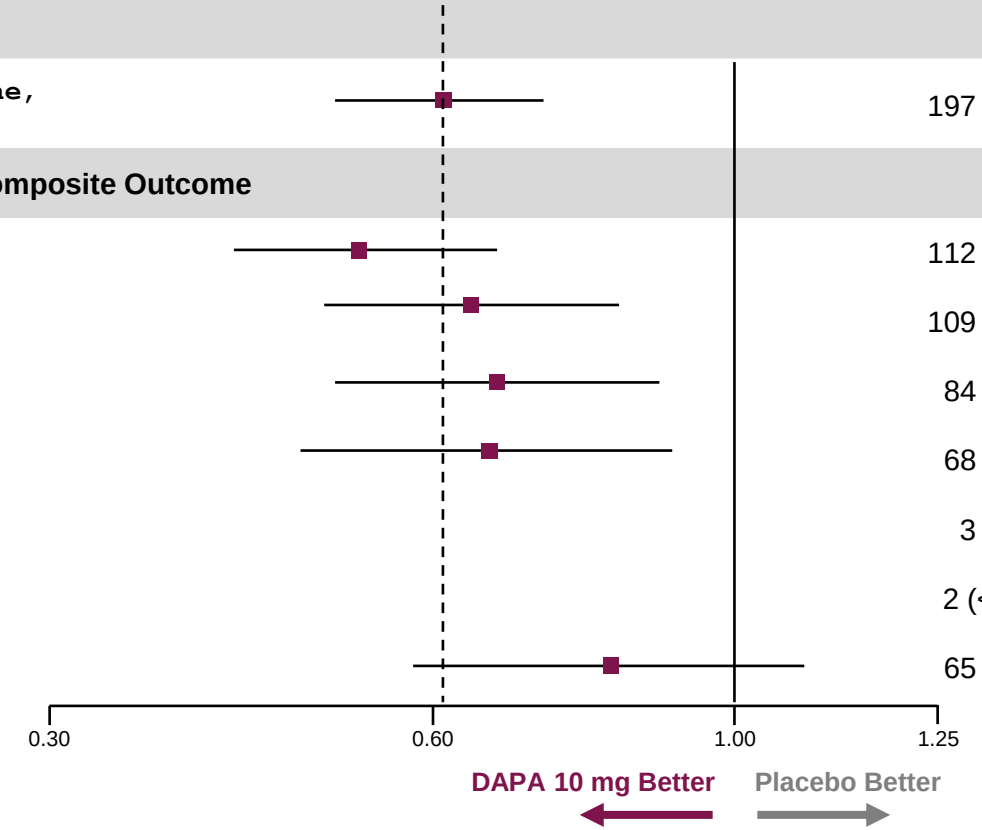
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

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: All Components Contributed to the Observed Treatment Effect[1]

	Number of Events (%)				
HR (95% CI)	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



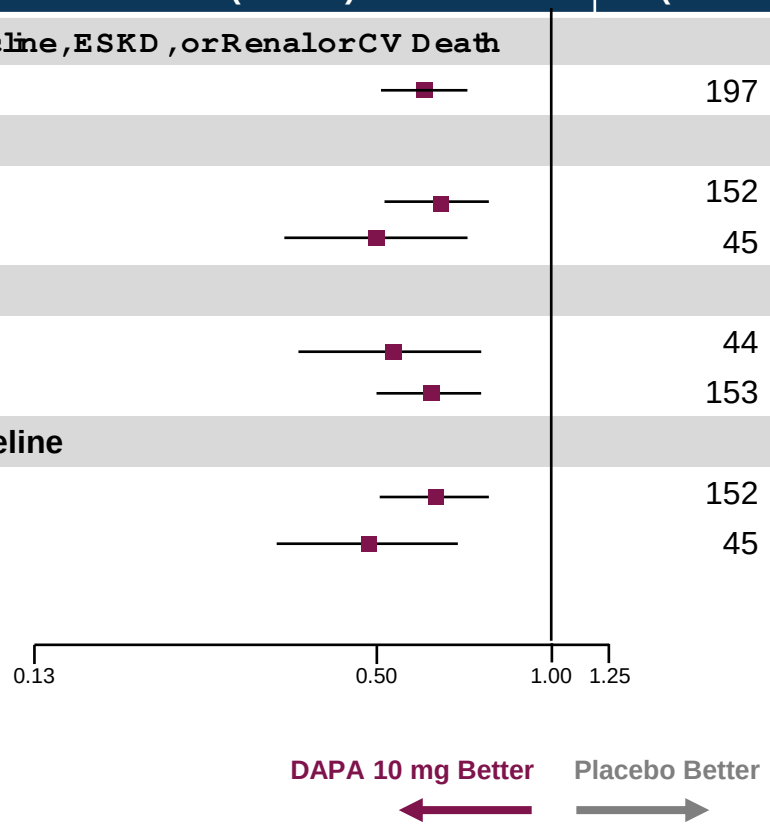
[a]There were 69 endpoint events for dapagliflozin and 100 endpoint events for placebo for the combined chronic dialysis and renal transplantation endpoint (HR 0.66; 95% CI 0.49, 0.90).

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: Treatment Benefit Consistent Across Prespecified Subgroups[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)	

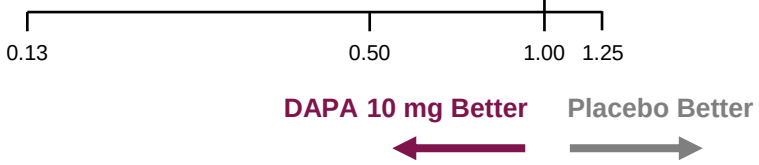


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

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: Treatment Benefit Consistent Across Prespecified Subgroups[1]

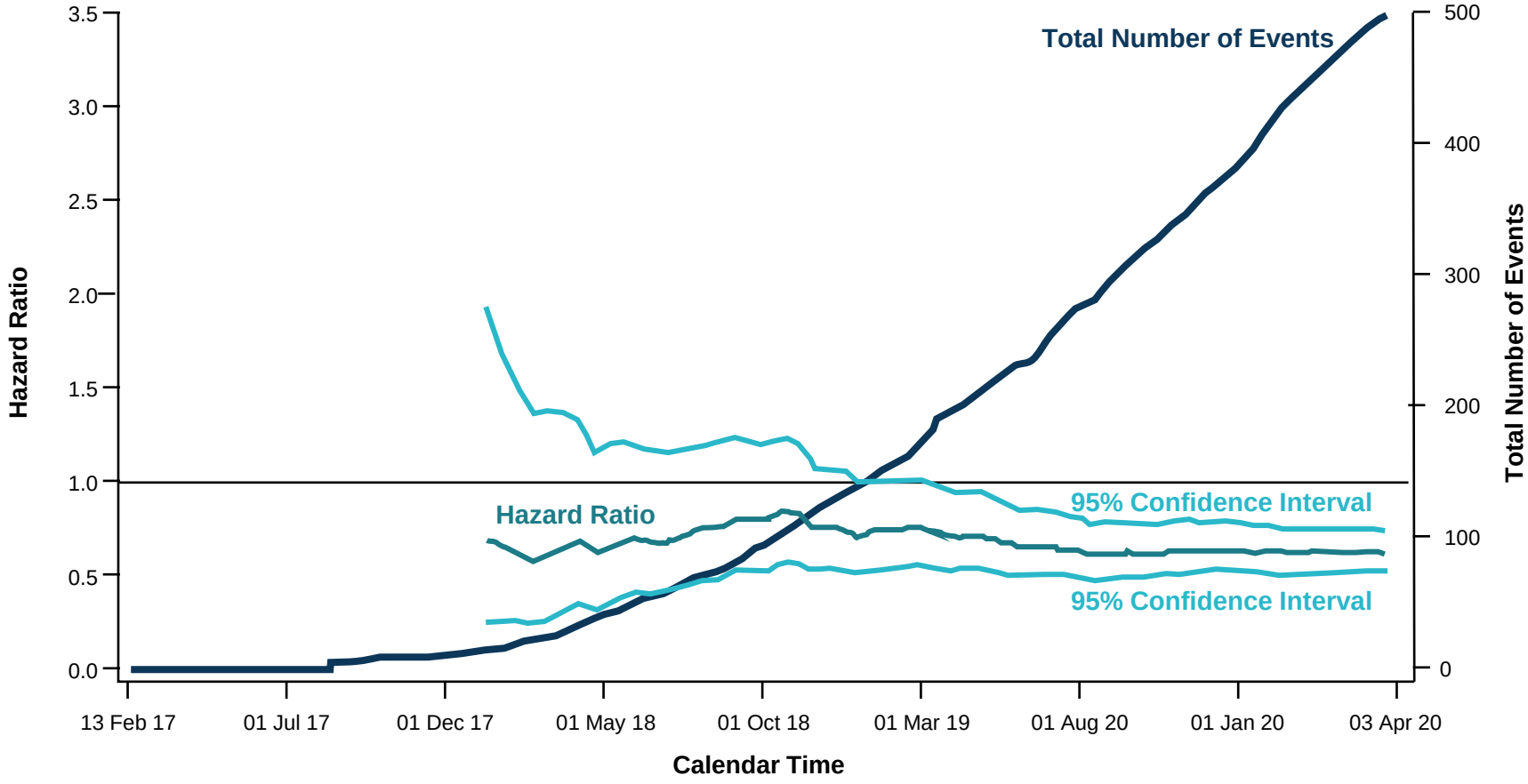
	Number of Events				
HR (95% CI)	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value Interaction[2]
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
Age (years)					0. 53
≤65	122	191	0.64	(0.51, 0.80)	
>65	75	121	0.58	(0.43, 0.77)	
Gender					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.

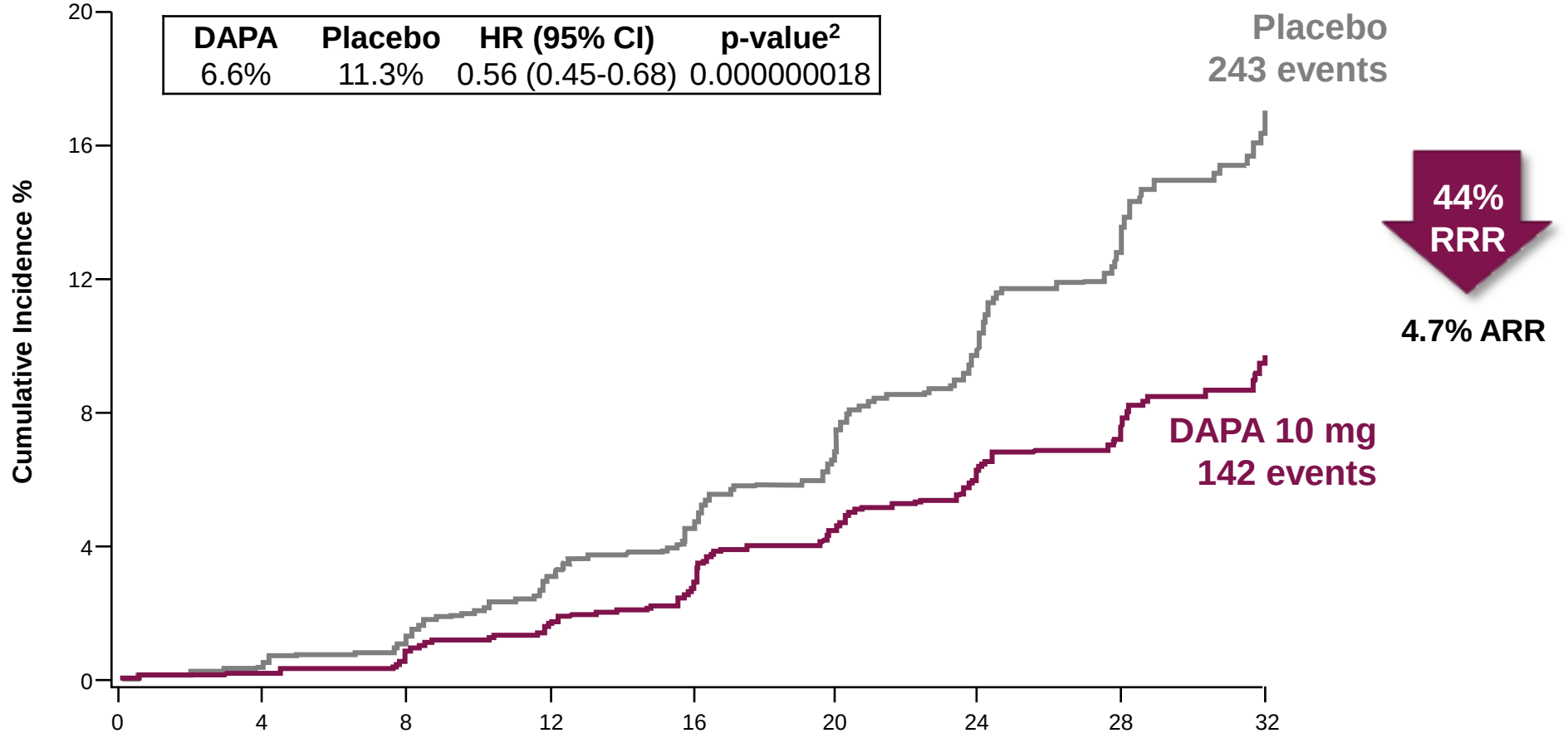
Evidence of Treatment Effect on the Primary Endpoint Emerged Early and was Consistent During the Trial[a]



[a]HR, 95%CI are from the same Cox proportional hazards model as for the primary analysis, and only included primary endpoint events.

Heerspink HL. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

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



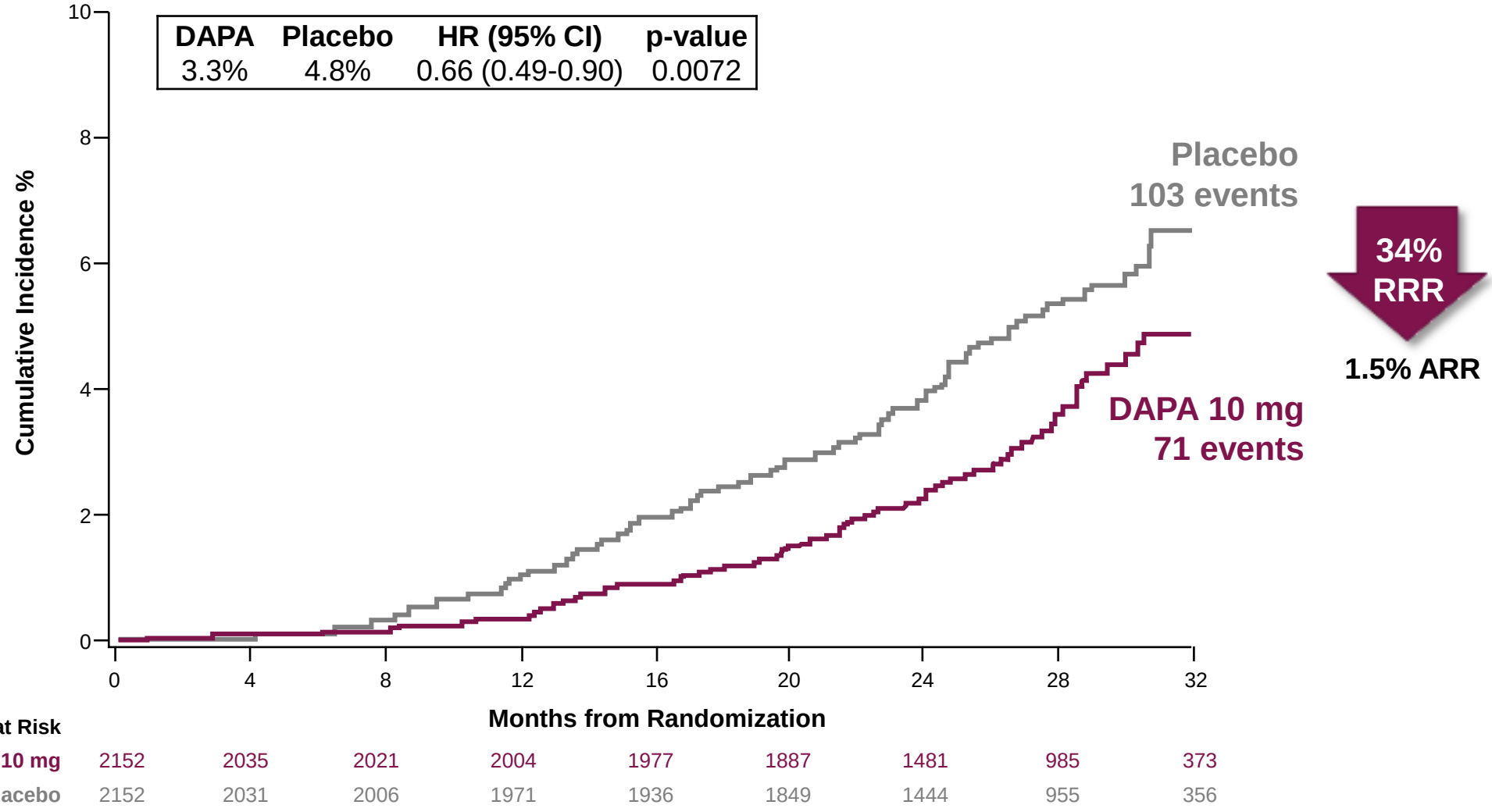
N at Risk									
DAPA 10 mg	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

[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.

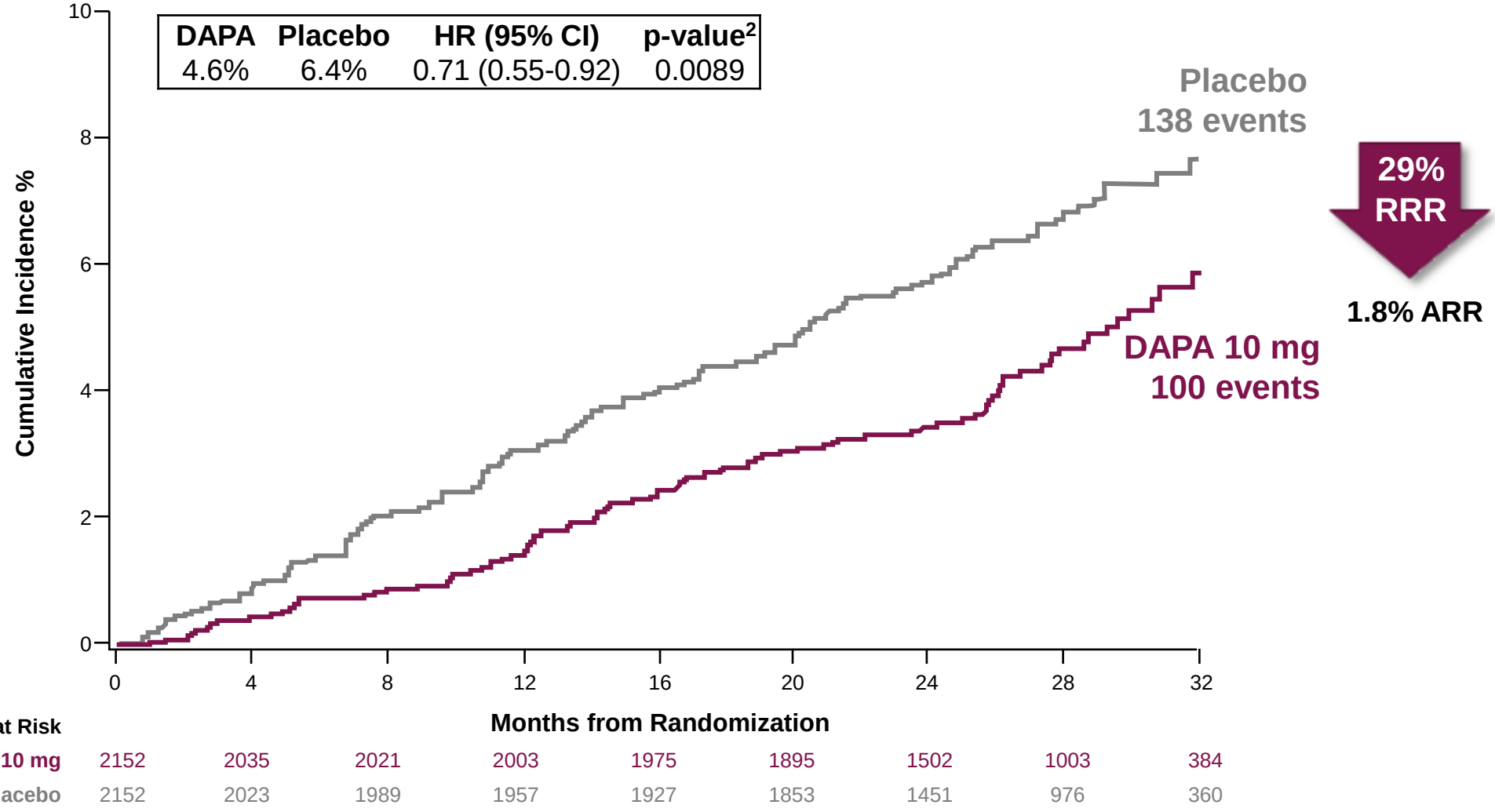
Exploratory Composite Outcome: Chronic Dialysis, Kidney Transplantation, or Renal Death[1,2]



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.

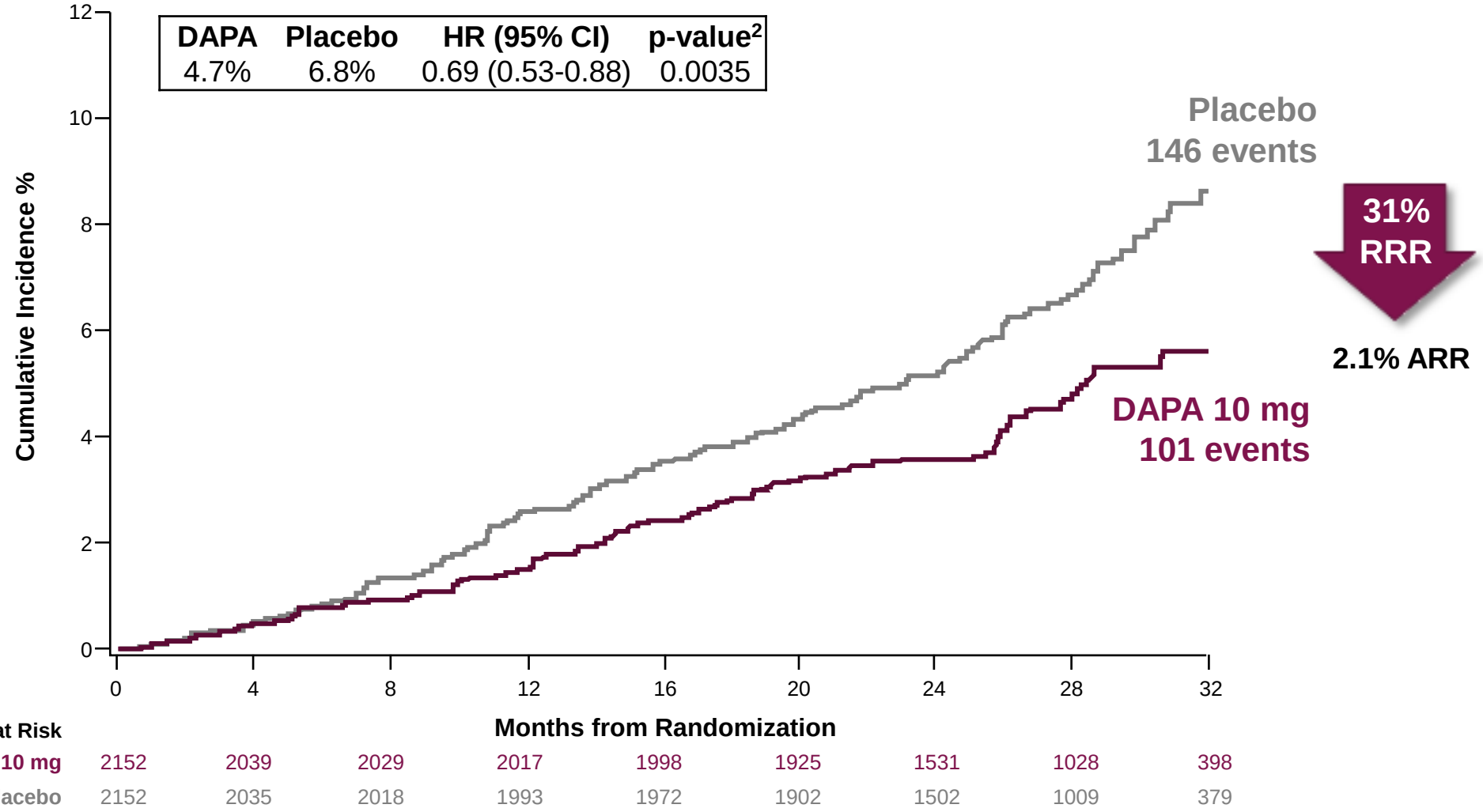
Secondary Composite Outcome: CV Death or Hospitalization for Heart Failure[1]



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]

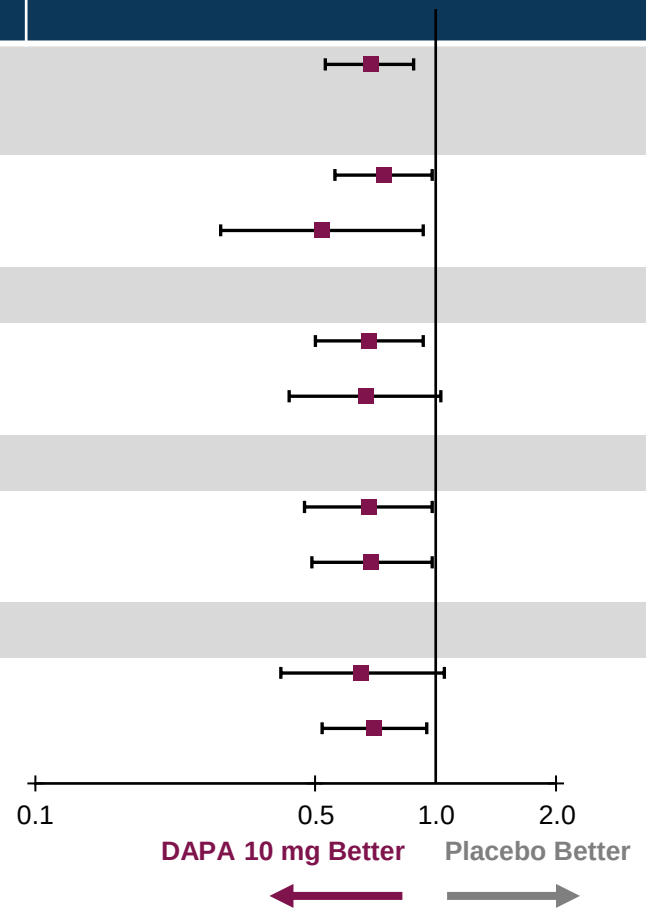


ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

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.

Secondary Outcome – All-cause Mortality: Treatment Benefit Consistent Across Prespecified Subgroups[1]

	No. of Patients/Total No.		Events per 100 Patient-years		Hazard Ratio (95% CI)	p-value for Interaction
	DAPA	Placebo	DAPA	Placebo		
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)	

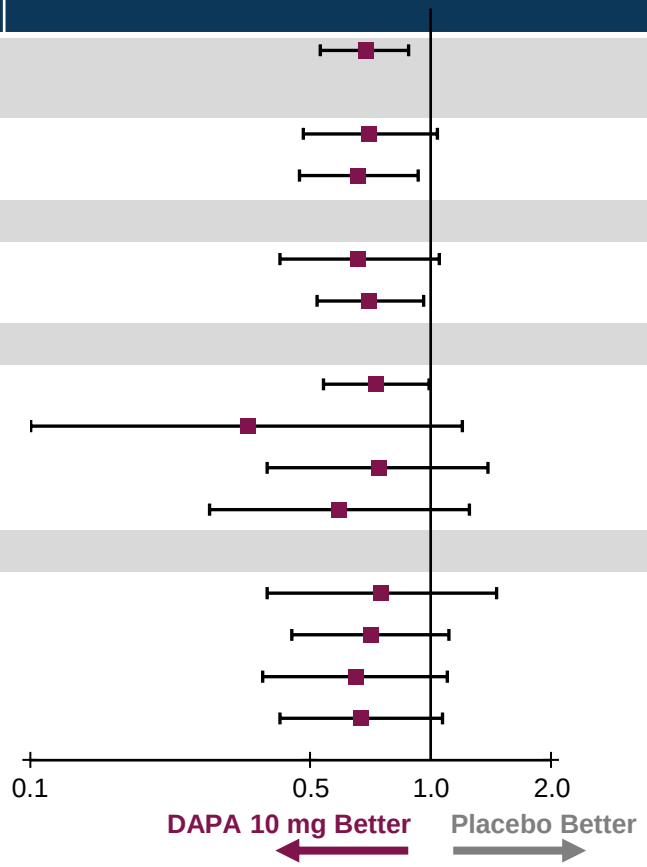


DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate.

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

Secondary Outcome – All-cause Mortality: Treatment Benefit Consistent Across Prespecified Subgroups[1]

	No. of Patients/Total No.		Events per 100 Patient-years		Hazard Ratio (95% CI)	p-value for Interaction
	DAPA	Placebo	DAPA	Placebo		
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)	

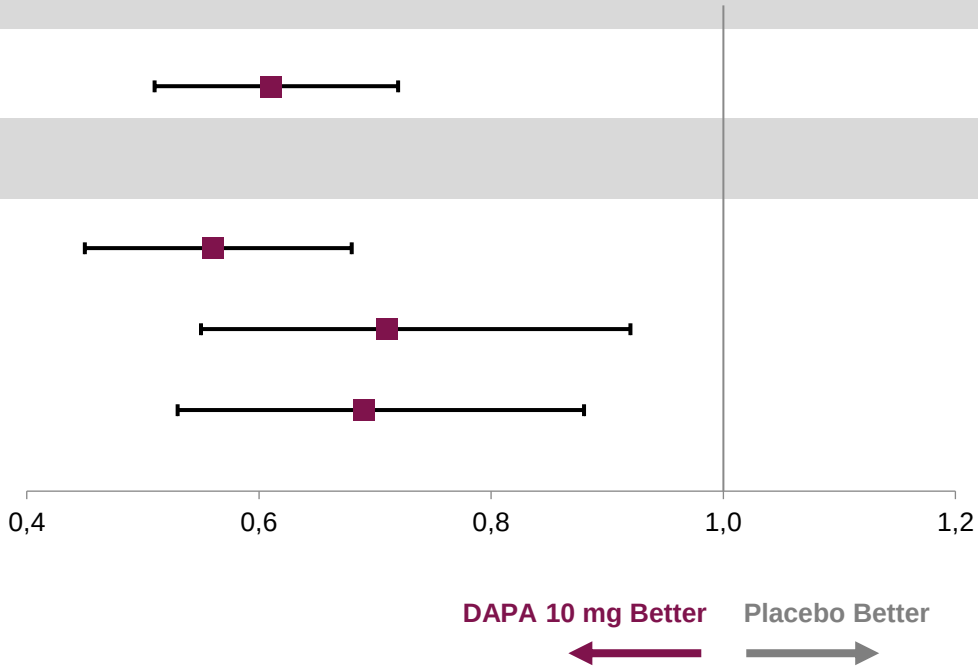


DAPA = dapagliflozin; No = number;

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

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

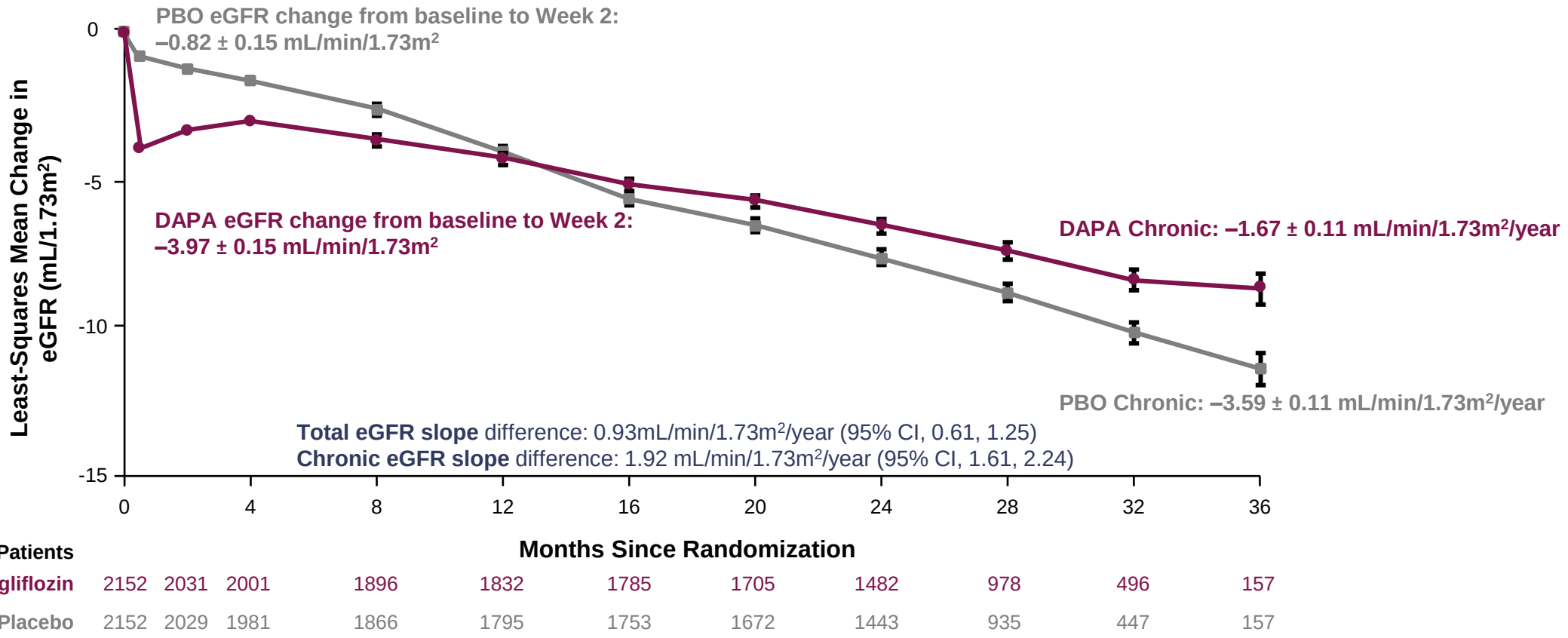
	Number of Events (%)				
HR (95% CI)	DAPA 10 mg (n=2152)	Placebo (n=2152)	Hazard Ratio	95% CI	p-value[2]
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, and Renal or CV Death	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	<0.0001
Secondary Outcomes					
Composite of ≥50% eGFR Decline, ESKD, 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.

Change from Baseline in eGFR[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

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.

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
for the primary composite endpoint (≥50% sustained decline in eGFR, ESKD, renal or CV death)

44% RRR
for the renal composite (≥50% sustained decline in eGFR, ESKD, or renal death)

29% RRR
for the composite of CV death or hospitalization for heart failure

31% RRR
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/1.73m^2	HFrEF eGFR ≥30 mL/min/1.73m^2	CKD eGFR ≥25 to ≤75 mL/min/1.73m^2
Glycemic Status	With T2D	With (45%) or Without (55%) T2D	With (68%) or Without (32%) T2D
Mean eGFR	85.2 mL/min/1.73m^2	66 mL/min/1.73m^2	43 mL/min/1.73m^2
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,orRenalor 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.

Additional Analyses

DAPA-CKD Subgroup Analysis
T2D Status

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to baseline T2D status

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

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

Demographics and Baseline Characteristics by Diabetes Status at Baseline (All Randomized Patients)

	Type 2 Diabetes		Without Type 2 Diabetes	
Characteristic[1]	**Dapagliflozin 10 mg (n=1455)**	**Placebo (n=1451)**	**Dapagliflozin 10 mg (n=697)**	**Placebo (n=701)**
Age (years), mean (SD)	64.1 (9.8)	64.7 (9.5)	56.9 (14.6)	56.0 (14.6)
Female sex, n (%)	494 (34)	471 (32)	215 (31)	245 (35)
Race, n (%)				
White	751 (52)	790 (54)	373 (54)	376 (54)
Black or African American	76 (5)	61 (4)	28 (4)	26 (4)
Asian	481 (33)	451 (31)	268 (38)	267 (38)
Other	147 (10)	149 (10)	28 (4)	32 (5)
Weight (kg), mean (SD)	83.2 (20.9)	83.8 (21.2)	77.9 (17.8)	78.3 (19.9)
BMI, kg/m^2, mean	30.3[2,a]		27.9[2,b]	
Current smoker, n (%)	195 (13)	200 (14)	88 (13)	101 (14)
Blood pressure (mmHg), mean (SD)				
Systolic	138.8 (17.6)	139.6 (17.1)	132.3 (16.4)	132.9 (16.9)
Diastolic	76.5 (10.4)	76.5 (9.9)	79.6 (10.9)	79.6 (10.8)
Hemoglobin (g/L), mean (SD)	126.3 (17.8)	125.6 (18.0)	133.4 (17.9)	132.7 (17.2)
Serum potassium (mmol/L), mean (SD)	4.7 (0.6)	4.7 (0.6)	4.6 (0.5)	4.6 (0.5)

[a] n=2899; [b] n=1397.

BMI = body mass index; T2D = Type 2 diabetes.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Renal Characteristics by Diabetes Status at Baseline (All Randomized Patients)

	Type 2 Diabetes		Without Type 2 Diabetes	
Characteristic[1]	**Dapagliflozin 10 mg (n=1455)**	**Placebo (n=1451)**	**Dapagliflozin 10 mg (n=697)**	**Placebo (n=701)**
Serum creatinine, mg/dL, mean	1.6[2]		1.8[2]	
eGFR (mL/min/1.73m²)	44.0 (12.6)	43.6 (12.6)	41.7 (11.5)	41.8 (11.9)
eGFR ≥60 mL/min/1.73m², n (%)	179 (12)	169 (12)	55 (8)	51 (7)
eGFR 45 to <60 mL/min/1.73m², n (%)	450 (31)	468 (32)	196 (28)	214 (31)
eGFR 30 to <45 mL/min/1.73m², n (%)	636 (44)	603 (42)	343 (49)	316 (45)
eGFR <30 mL/min/1.73m², n (%)	190 (13)	211 (15)	103 (15)	120 (17)
UACR (mg/g), median (IQR)	1024.5 (472.5-2111.0)	1004.5 (493.3-2017.0)	870.5 (472.0-1533.5)	841.5 (458.5-1554.5)
UACR 30-300 mg/g (Stage A2), %	10.6[2]		9.7[2]	
UACR >300 mg/g (Stage A3), %	89.4[2]		90.3[2]	
UACR >1000 mg/g, n (%)	741 (51)	732 (50)	307 (44)	299 (43)

eGFR = estimated glomerular filtration rate; IQR = interquartile range; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Medical History and Baseline Medications by Diabetes Status at Baseline (All Randomized Patients)

	Type 2 Diabetes		Without Type 2 Diabetes	
Characteristic[1]	Dapagliflozin 10 mg (n=1455)	Placebo (n=1451)	Dapagliflozin 10 mg (n=697)	Placebo (n=701)
HbA1c (%), mean (SD)	7.8 (1.7)	7.8 (1.6)	5.6 (0.4)	5.6 (0.4)
HbA1c (mmol/mol), mean (SD)	62 (18.6)	62 (17.5)	38 (4.4)	38 (4.4)
Obese (BMI ≥30 kg/m²), %	49.4[2]		34.3[2]	
Hypertension, %	98.3[2]		90.5[2]	
Any history of CV disease, %	44.1[2]		23.5[2]	
Myocardial infarction, %	11.0[2]		5.1[2]	
Stroke, %	7.9[2]		4.9[2]	
Heart failure, n (%)	177 (12)	184 (13)	58 (8)	49 (7)
Prior medication, n (%)				
ACE inhibitor	451 (31)	443 (31)	222 (32)	238 (34)
ARB	984 (68)	974 (67)	460 (66)	452 (64)
Diuretic	718 (49)	747 (51)	210 (30)	207 (30)
Statin	1039 (71)	1043 (72)	356 (51)	356 (51)
Metformin (biguanides)[c]	629 (44)	613 (43)	-	-
SU derivative[c]	389 (27)	385 (27)	-	-
DPP4 inhibitor[c]	364 (25)	378 (26)	-	-
GLP-1 analog[c]	63 (4)	59 (4)	-	-
Insulin[a]	814 (56)	784 (54)	-	-

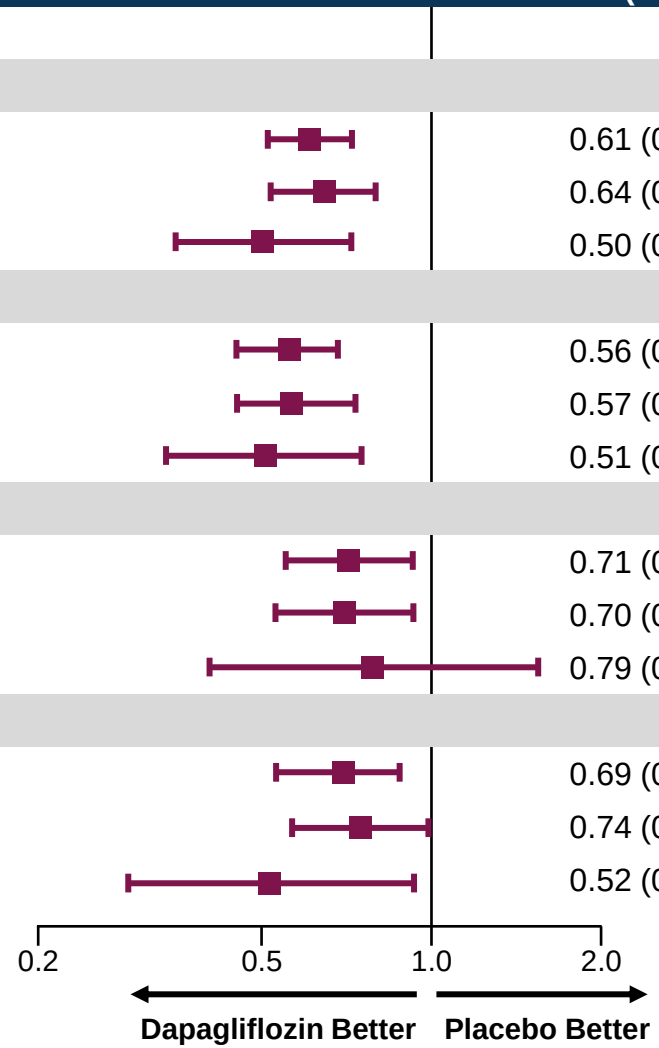
[a]Dapagliflozin n=1444; placebo n=1442.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; DPP4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Primary and Secondary Outcomes by Diabetes Status

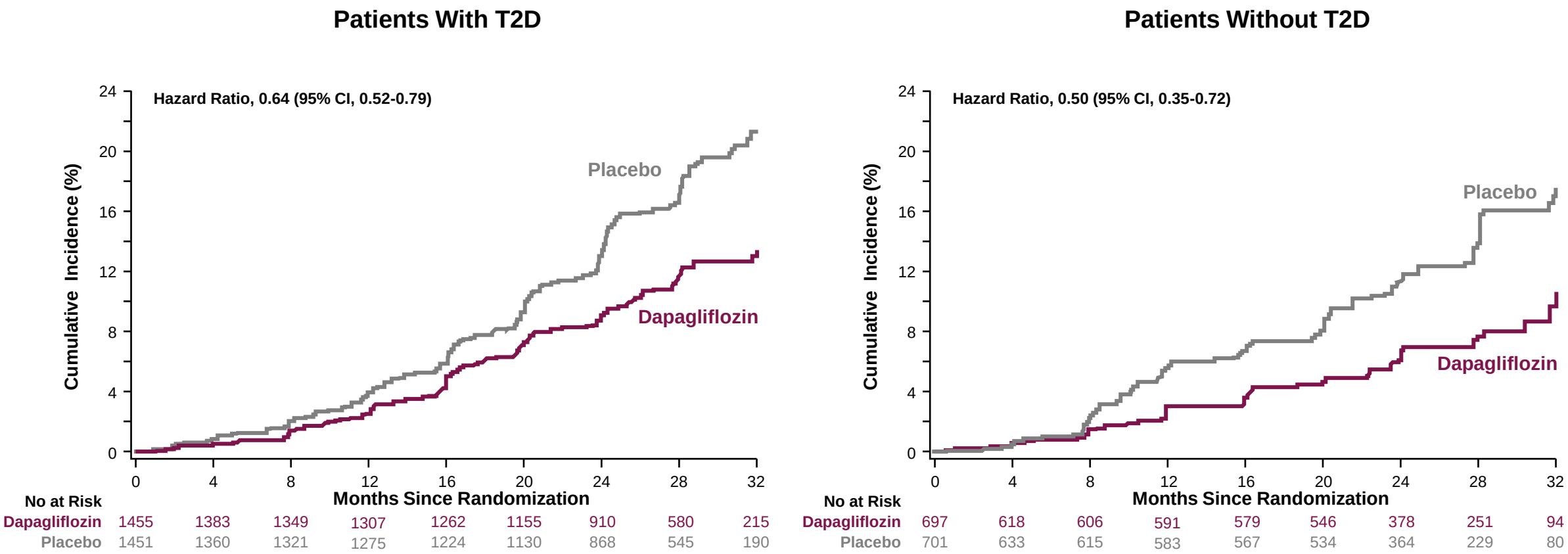
	Dapagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients with event/total no. patients			
Primary outcome				0.24
Overall	197/2152	312/2152	0.61 (0.51, 0.72)	
With type 2 diabetes	152/1455	229/1451	0.64 (0.52, 0.79)	
Without type 2 diabetes	45/697	83/701	0.50 (0.35, 0.72)	
Renal-specific outcome				0.57
Overall	142/2152	243/2152	0.56 (0.45, 0.68)	
With type 2 diabetes	103/1455	173/1451	0.57 (0.45, 0.73)	
Without type 2 diabetes	39/697	70/701	0.51 (0.34, 0.75)	
CV death or hHF				0.78
Overall	100/2152	138/2152	0.71 (0.55, 0.92)	
With type 2 diabetes	85/1455	119/1451	0.70 (0.53, 0.92)	
Without type 2 diabetes	15/697	19/701	0.79 (0.40, 1.55)	
All-cause mortality				0.25
Overall	101/2152	146/2152	0.69 (0.53, 0.88)	
With type 2 diabetes	84/1455	113/1451	0.74 (0.56, 0.98)	
Without type 2 diabetes	17/697	33/701	0.52 (0.29, 0.93)	



CV = cardiovascular; hHF = hospitalization for heart failure; T2D = type 2 diabetes.

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

Primary Outcome (Sustained ≥50% eGFR Decline,ESKD,RenalorCV Death[a]) by Diabetes Status



p-interaction=0.24

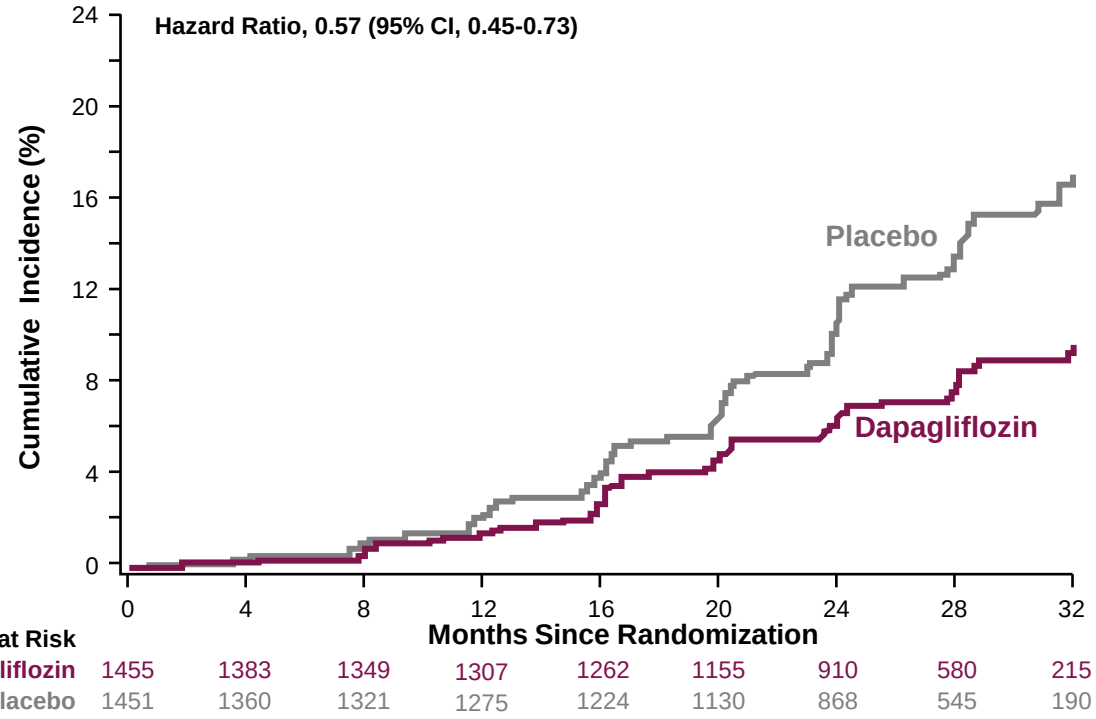
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

CV= cardiovascular; ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

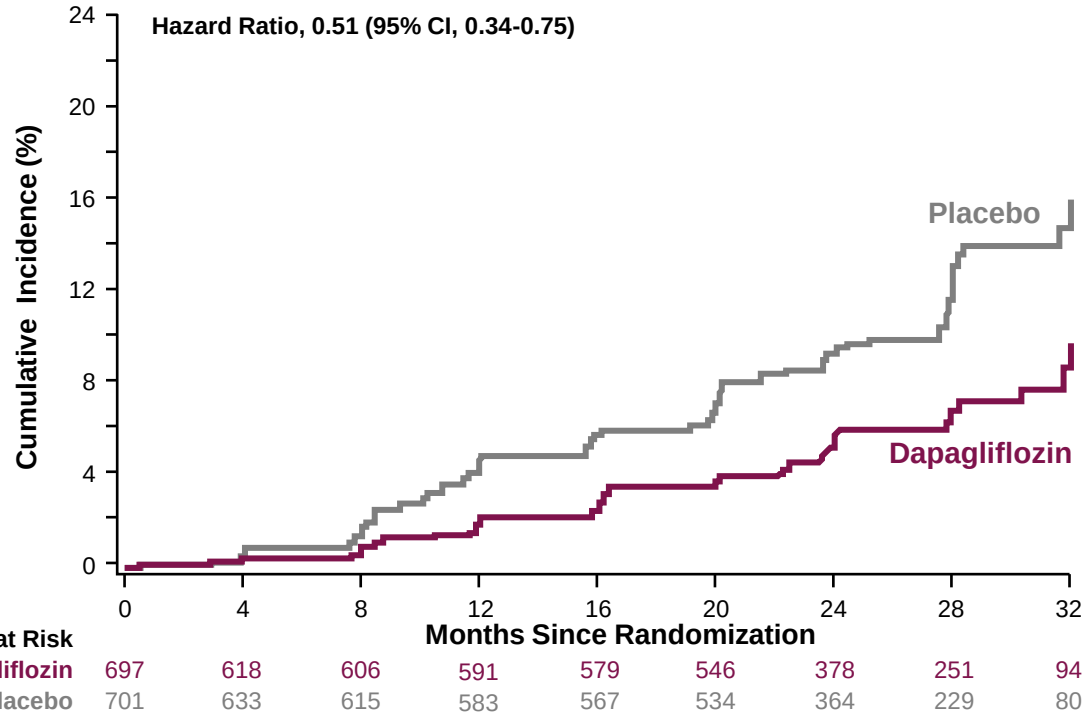
Secondary Renal-Specific Composite Outcome (Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a]) by Diabetes Status

Patients With T2D



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

Patients Without T2D



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

p-interaction=0.57

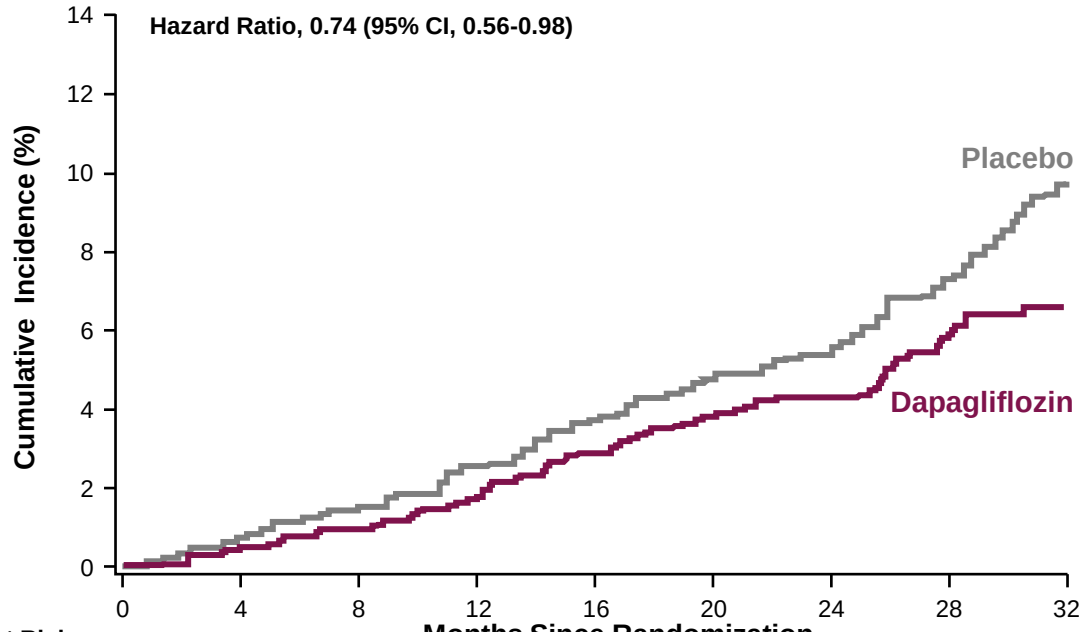
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

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

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

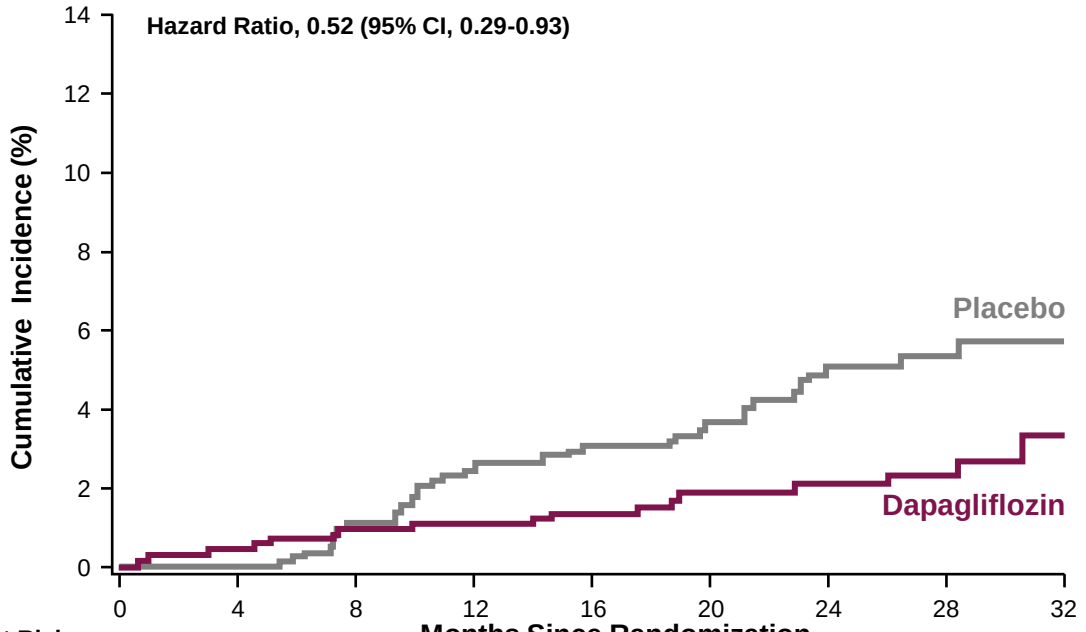
Secondary Outcome (All-Cause Mortality) by Diabetes Status

Patients With T2D



No at Risk									
Dapagliflozin	1455	1404	1397	1386	1369	1315	1092	737	285
Placebo	1451	1390	1380	1364	1348	1297	1076	725	273

Patients Without T2D



No at Risk									
Dapagliflozin	697	635	632	631	629	610	439	291	113
Placebo	701	645	638	629	624	605	426	284	106

p-interaction=0.25

T2D = type 2 diabetes

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

Safety by Diabetes Status

Safety outcomes[a], %	With T2D			Without T2D			
	Dapagliflozin 10 mg (n=1453)	Placebo (n=1450)	Odds Ratio (95% CI)	Dapagliflozin 10 mg (n=696)	Placebo (n=699)	Odds Ratio (95% CI)	p-interaction
Discontinuation due to AE	6	6	0.86 (0.63, 1.17)	5	4	1.26 (0.77, 2.09)	0.20
Any serious AE[b]	33	39	0.79 (0.68, 0.92)	22	24	0.88 (0.68, 1.12)	0.48
AE of special interest							
Amputation[c]	2	3	0.92 (0.57, 1.46)	0	<1%	NA	0.26
Any definite or probable DKA	0	<1%	NA	-	-	-	NA
Fracture[d]	4	4	1.28 (0.89, 1.87)	3	3	1.12 (0.59, 2.15)	0.72
Renal-related adverse event[d]	8	10	0.80 (0.62, 1.03)	5	6	0.85 (0.53, 1.35)	0.83
Major hypoglycemia[e]	1	2	0.49 (0.25, 0.93)	-	-	-	1.00
Volume depletion[d]	6	5	1.31 (0.96, 1.81)	5	3	1.90 (1.09, 3.41)	0.27

[a]Safety analysis set; [b]Includes death; [c]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; [d]Based on pre-defined list of preferred terms; [e]AE 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.

AE = adverse event; DKA = diabetic ketoacidosis; NA = not applicable; T2D = type 2 diabetes.

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

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

There were no deaths due to UTI or genital infections

[a]Safety 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.

Summary

- In this prespecified analysis, dapagliflozin reduced the risk of renal events, CV events, and all-cause mortality, regardless of T2D status
- Dapagliflozin was well tolerated; the safety profile was consistent in patients with and without T2D
  - SAEs of genital and and urinary tract infections were low
  - Genital and urinary tract infection SAEs were more frequent with dapagliflozin than placebo and in the T2D patient subgroup than in patients without T2D
  - There were few discontinuations due to AEs of urinary tract infections or genital infection

CV = cardiovascular; SAE = serious adverse events; T2D = type 2 diabetes.

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

DAPA-CKD Subgroup Analysis
Etiology

In a prespecified 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

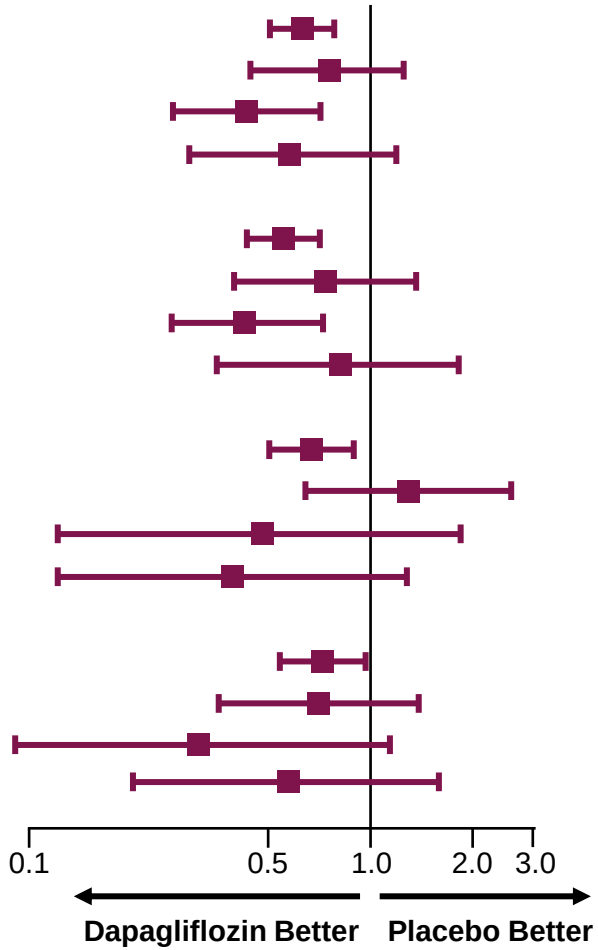
Characteristic	Diabetic Nephropathy		Ischemic / Hypertensive CKD		Glomerulonephritis		Other / Unknown	
	DAPA (n=1271)	PBO (n=1239)	DAPA (n=324)	PBO (n=363)	DAPA (n=343)	PBO (n=352)	DAPA (n=214)	PBO (n=198)
Age, years, mean	64.2	65.0	64.2	63.1	51.9	51.7	59.6	58.4
Sex, female, %	34.2	33.0	26.9	27.5	34.1	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	139.1/76.4	139.8/76.2	137.9/79.6	139.5/79.5	128.8/79.0	128.6/78.2	133.9/78.6	134.6/80.7
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/g, median	1056.0	1037.5	801.0	711.0	975.0	981.2	794.5	841.0

CKD = chronic kidney disease; DAPA = dapagliflozin 10 mg; eGFR = estimated glomerular filtration rate; PBO = placebo; UACR = urinary albumin-to-creatine ratio.

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

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)	



[a]Event data are numbers of patients with an outcome event/total patients; [b]Sustained ≥50% eGFR decline, ESKD, renal or CV death; [c]Sustained ≥50% eGFR decline, ESKD, or renal death; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

Baseline Characteristics in Patients with IgA Nephropathy

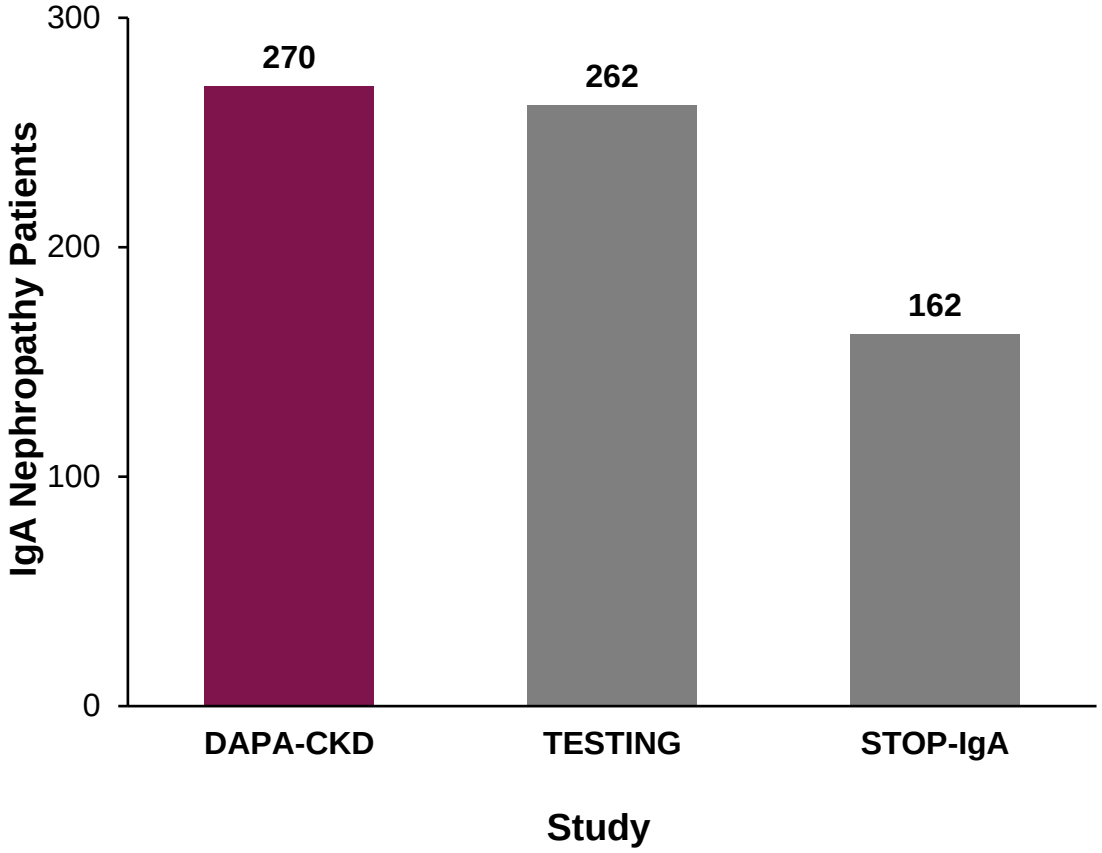
Characteristic	Dapagliflozin (n=137)	Placebo (n=133)	Total (n=270)
Age, years, mean	52	50	51
Sex, female, %	32	33	33
Race, %			
White	39	41	40
Black or African-American	0	1	0
Asian	60	58	59
Other	1	1	1
Weight, kg, mean	75	79	77
Systolic/diastolic blood pressure, mmHg, mean	128/79	127/80	127/79
eGFR, mL/min/1.73m^2, mean	44	43	44
UACR, mg/g, median	890	903	900
UACR ≤1000 mg/g, %	56	55	56
UACR >1000 mg/g, %	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

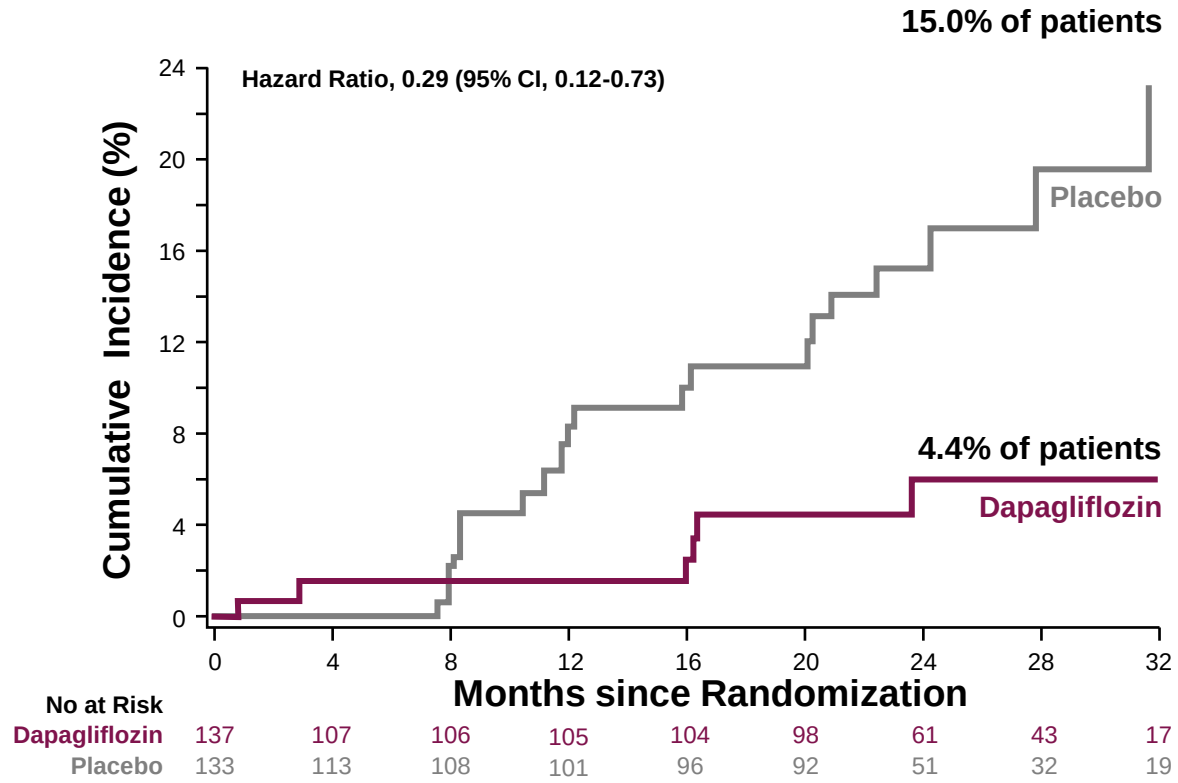
Heerspink HJL et al. Presented at: WCN; April 16-19, 2021; Virtual.

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]

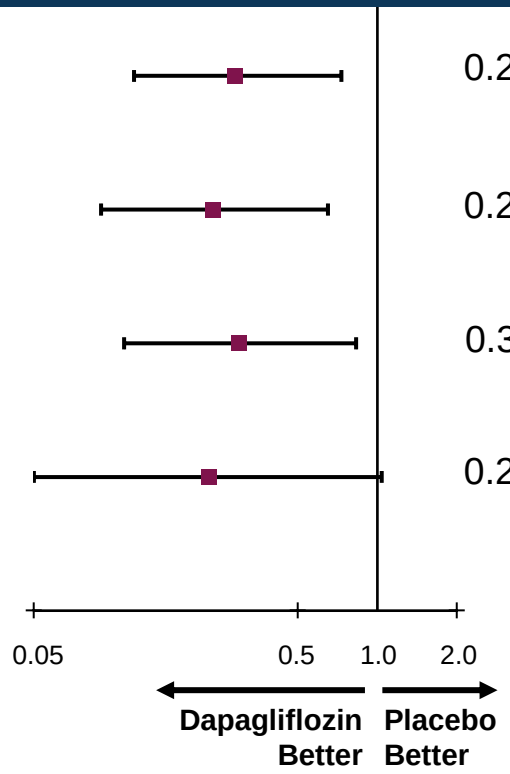


CKD = chronic kidney disease; IgA = immunoglobulin A

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

Key Endpoints in Patients with IgA Nephropathy

	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value
	No. of patients/total no.		Events/100 patient-years			
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.

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 *IgA nephropathy*[2]	343 137	351 133		
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 *IgA nephropathy*[2]	16 (4.7) 6 (4.4)	20 (5.7) 7 (5.3)	0.81 (0.41, 1.59)	
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 *IgA nephropathy*[2]	64 (18.7) 22 (16.1)	91 (25.9) 34 (25.6)	0.66 (0.46, 0.94)	
Other / Unknown	48 (22.5)	38 (19.3)	1.22 (0.76, 1.97)	

[a]Includes death.

CKD = chronic kidney disease; 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.

Summary

- In this prespecified analysis, dapagliflozin reduced the risk of renal events, CV events, and all-cause mortality, regardless of underlying cause of kidney disease
- In patients with IgA nephropathy, dapagliflozin reduced the risk of the primary composite endpoint, renal specific composite endpoint and progression to ESKD.
- 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; IgA = immunoglobulin A.

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

DAPA-CKD Subgroup Analysis
Stage 4 CKD

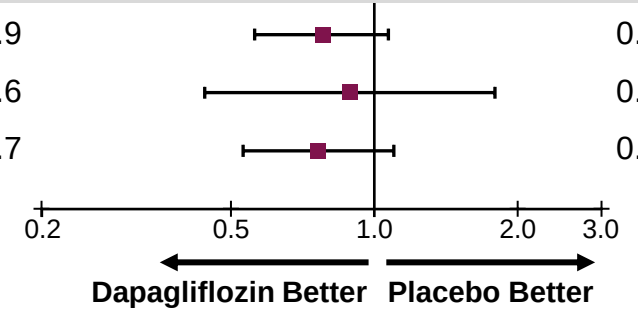
In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed by stage of CKD, including Stage 4 CKD (<30 ml/min/1.73m^2)

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)	



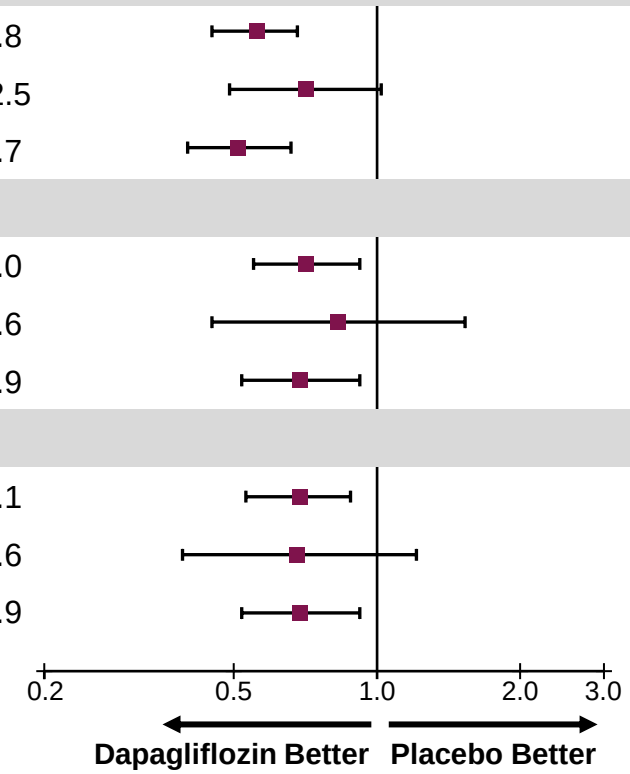
NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2

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

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

Secondary Outcomes According to CKD Stage

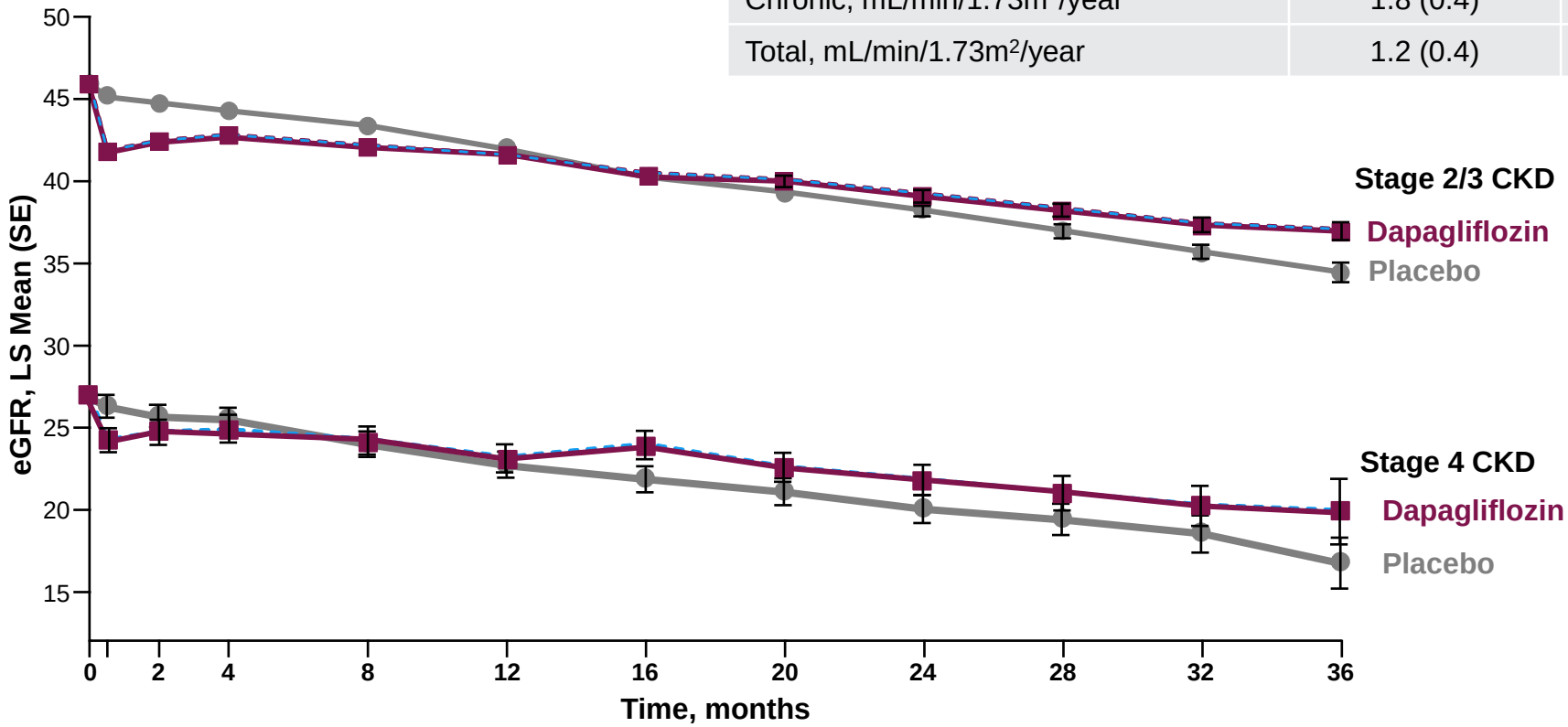
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients/ total no.		Events/100 patient-years			
Kidney composite outcome: ≥50% eGFR decline, ESKD, or kidney death						
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	
Stage 4	49/293	73/331	9.2	12.5	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. Presented at: WCN; April 16-19, 2021; Virtual.

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. Presented at: WCN; April 16-19, 2021; Virtual.

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. Presented at: WCN; April 16-19, 2021; Virtual.

Summary

- In this pre-specified analysis in patients with advanced CKD (Stage 4 CKD), dapagliflozin had similar reduction in major kidney and CV events when compared to those with Stage 2/3 CKD
- 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. Presented at: WCN; April 16-19, 2021; Virtual.

DAPA-CKD Subgroup Analysis
Baseline History of CVD

In a secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to baseline history of CVD

CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Baseline Characteristics by Baseline CVD History

	Baseline cardiovascular disease (n= 1610)		No baseline cardiovascular disease (n=2694)	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	n = 813	**n = 797**	**n = 1339**	**n = 1355**
Age – years	66.5	66.2	59	59.4
Male sex - no (%)	587 (72.2)	548 (68.8)	856 (63.9)	888 (65.5)
Race – no. (%)				
White	539 (66.3)	523 (65.6)	585 (43.7)	643 (47.5)
Black or African American	37 (4.6)	43 (5.4)	67 (5)	44 (3.2)
Asian	180 (22.1)	173 (21.7)	569 (42.5)	545 (40.2)
Other	57 (7.0)	58 (7.3)	118 (8.8)	123 (9.1)
Heart rate – beats/min = pulse	71.6	70.7	73.7	74.1
Systolic Blood Pressure – mmHg	138.8	139.7	135.5	136.1
HbA1c – %	7.4	7.4	6.9	6.8
Hemoglobin – g/dL	130.1	127.9	127.7	127.9
Current smoker – no. (%)	97 (11.9)	117 (14.7)	186 (13.9)	184 (13.6)
Body-mass index – Kg/m^2	30.3	30.9	28.8	28.9
Obese (body-mass index ≥30 Kg/m^2) – no. (%)	415 (51.0)	435 (54.6)	526 (39.3)	541 (39.9)
eGFR – ml/min/1.73m^2 of body-surface area	43.3	43.0	43.2	42.9
eGFR category				
≥60 ml/min/1.73m^2 – no. (%)	94 (11.6)	88 (11.0)	140 (10.5)	132 (9.7)
45-59 ml/min/1.73m^2 – no. (%)	233 (28.7)	254 (31.9)	413 (30.8)	428 (31.6)
30-44 ml/min/1.73m^2 – no. (%)	388 (47.7)	322 (40.4)	591 (44.1)	597 (44.1)
<30 ml/min/1.73m^2 – no. (%)	98 (12.1)	133 (16.7)	195 (14.6)	198 (14.6)
Median UACR (IQR) – mg/g	1012 (446-1956)	944 (473-1825)	937 (487-1856)	933 (488-1911)

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

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Baseline Medical History by Baseline CVD History

	Baseline cardiovascular disease, n (%) (n= 1610)		No baseline cardiovascular disease, n (%) (n=2694)	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
	n = 813	n = 797	n = 1339	n = 1355
Any atherosclerotic cardiovascular disease	663 (81.5)	666 (83.6)	-	-
Hypertension	803 (98.8)	788 (98.9)	1262 (94.2)	1268 (93.6)
Heart failure	235 (28.9)	233 (29.2)	-	-
Atrial fibrillation or flutter	115 (14.1)	112 (14.1)	-	-
Angina	201 (24.7)	204 (25.6)	-	-
Myocardial infarction	185 (22.8)	207 (26.0)	-	-
Coronary artery bypass grafting	74 (9.1)	102 (12.8)	-	-
Percutaneous coronary intervention	145 (17.8)	149 (18.7)	-	-
Stroke	144 (17.7)	154 (19.3)	-	-
Transient ischemic attack	41 (5.0)	38 (4.8)	-	-
Peripheral artery disease	154 (18.9)	171 (21.5)	-	-
Amputation	59 (7.3)	50 (6.3)	36 (2.7)	36 (2.7)
Type 2 diabetes	640 (78.7)	641 (80.4)	815 (60.9)	810 (59.8)

CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Baseline Therapy by Baseline CVD History

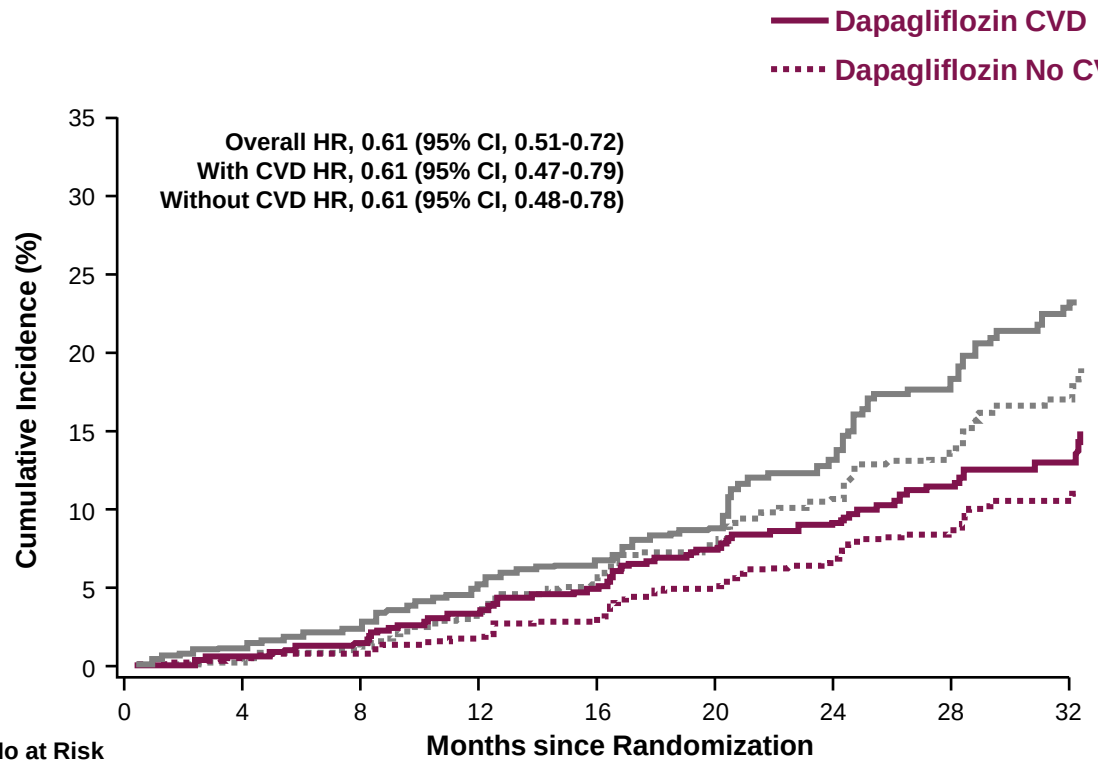
	Baseline cardiovascular disease (n= 1610)		No baseline cardiovascular disease (n=2694)	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	n = 813	**n = 797**	**n = 1339**	**n = 1355**
Device therapy – no (%)				
Implantable cardioverter-defibrillator	8 (1.0)	6 (0.8)	-	-
Cardiac resynchronization therapy	2 (0.2)	4 (0.5)	-	-
Pacemaker	27 (3.3)	28 (3.5)	-	-
Cardiovascular and renal medication – no (%)				
Beta-blocker	495 (60.9)	474 (59.5)	351 (26.2)	360 (26.6)
Diuretic	437 (53.8)	443 (55.6)	491 (36.7)	511 (37.7)
Mineralocorticoid receptor antagonist	65 (8.0)	74 (9.3)	44 (3.3)	46 (3.4)
ACE inhibitor, ARB or other RAS blocker	798 (98.2)	761 (95.5)	1296 (96.8)	1319 (97.3)
Antiplatelet	577 (71.0)	547 (68.6)	375 (28.0)	381 (28.1)
Statin	622 (76.5)	609 (76.4)	773 (57.7)	790 (58.3)
Other lipid lowering therapy	132 (16.2)	115 (14.4)	188 (14.0)	210 (15.5)
Glucose-lowering medication – no (%)				
Biguanide	272 (33.5)	274 (34.4)	362 (27.0)	342 (25.2)
Sulfonylurea	158 (19.4)	156 (19.6)	232 (17.3)	230 (17.0)
DPP-4 inhibitor	133 (16.4)	145 (18.2)	231 (17.3)	233 (17.2)
GLP-1 receptor agonist	30 (3.7)	23 (2.9)	33 (2.5)	36 (2.7)
Insulin	382 (47.0)	367 (46)	432 (32.3)	417 (30.8)

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CVD = cardiovascular disease; DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon like peptide-1; RAS = renin-angiotensin system.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

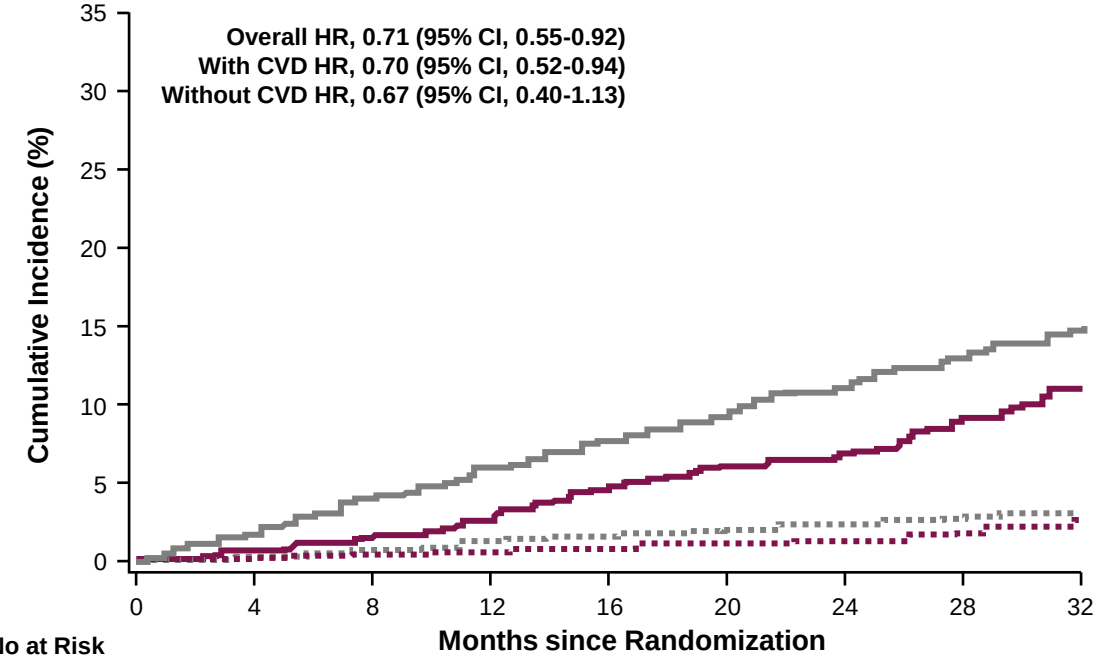
Outcomes by Baseline CVD

Primary Endpoint
eGFR Decline ≥50% ,ESKD,RenalDeath,orCV Death



No at Risk									
Dapagliflozin/CVD	813	780	760	736	710	650	510	326	124
Dapagliflozin/No CVD	1339	1221	1195	1162	1131	1051	778	505	185
Placebo/CVD	797	757	734	703	677	626	470	289	94
Placebo/No CVD	1355	1236	1202	1155	1114	1038	762	485	176

Secondary Endpoint
hHF or CV Death



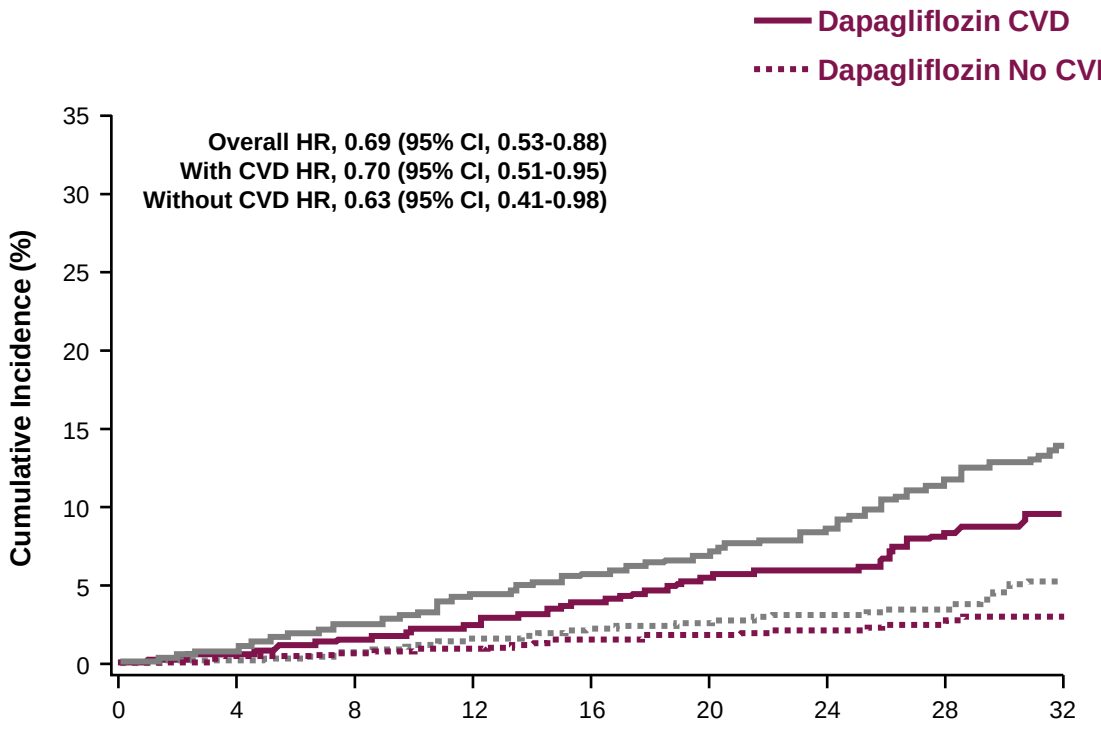
No at Risk									
Dapagliflozin/CVD	813	787	779	767	747	712	581	384	150
Dapagliflozin/No CVD	1339	1248	1242	1236	1228	1183	921	619	234
Placebo/CVD	797	761	740	721	703	671	531	366	124
Placebo/No CVD	1355	1262	1249	1236	1224	1182	920	610	236

CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

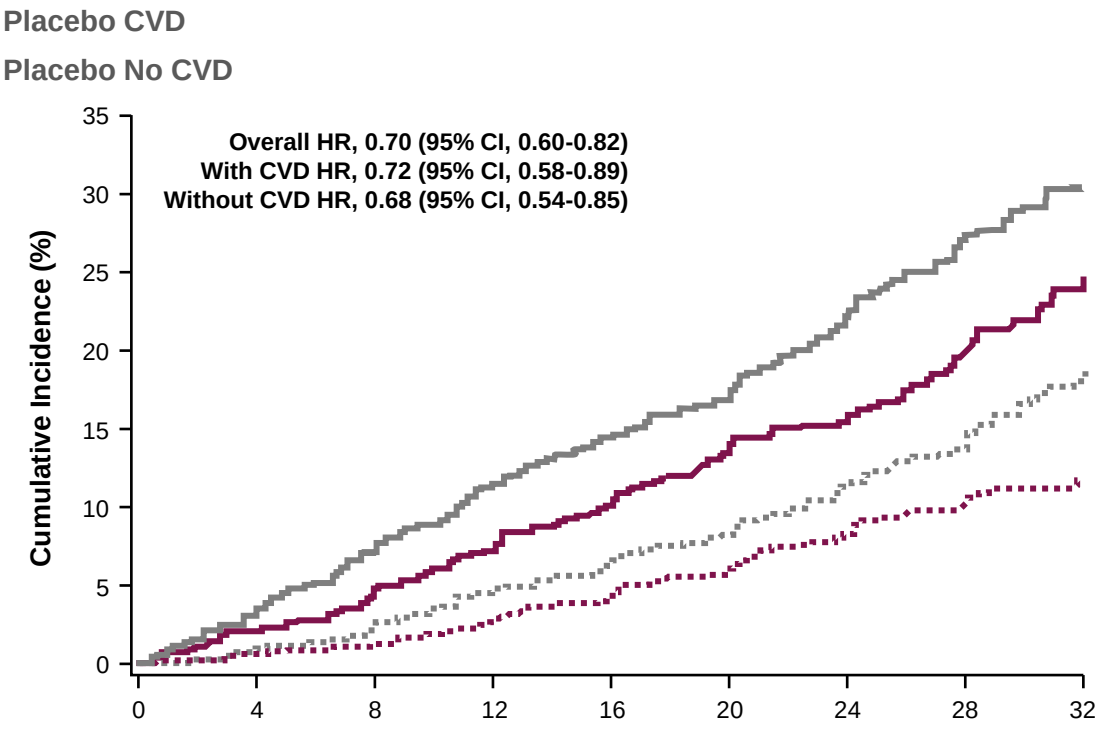
Outcomes by Baseline CVD

Secondary Endpoint
All-cause Mortality



No at Risk									
Dapagliflozin/CV	813	790	783	776	764	731	600	403	160
Dapagliflozin/No CV	1339	1249	1246	1241	1234	1194	931	625	238
Placebo/CV	797	770	759	745	734	702	566	386	137
Placebo/No CV	1355	1265	1259	1248	1238	1200	936	623	242

***Post Hoc* Endpoint**
MI, Stroke, hHF, ESKD, or Death



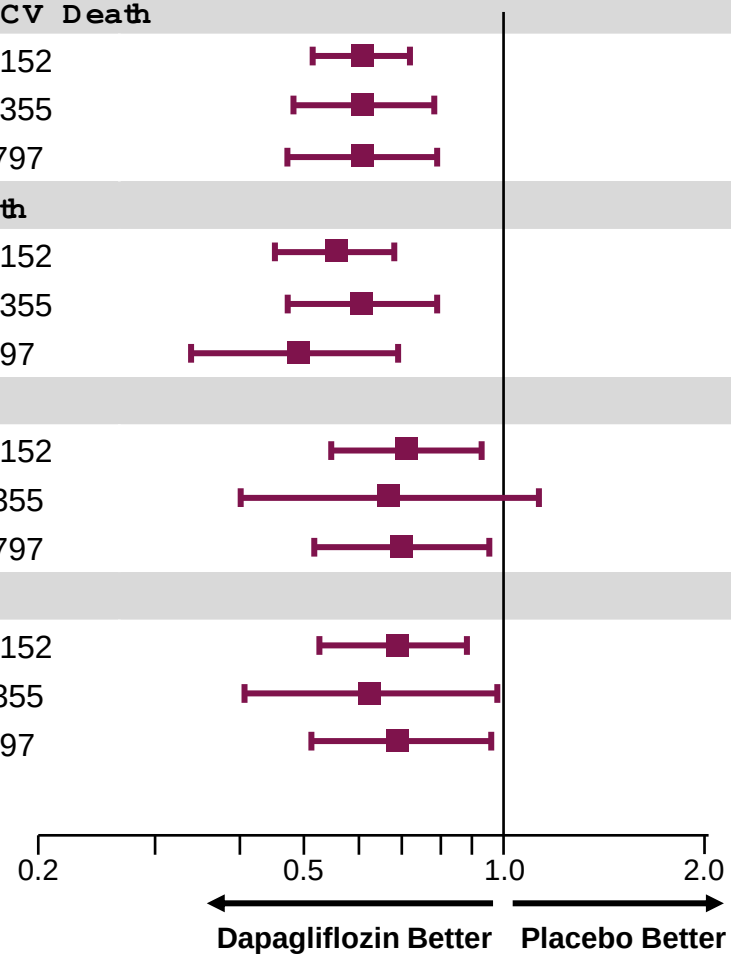
No at Risk									
Dapagliflozin/CV	813	771	747	715	687	627	493	305	114
Dapagliflozin/No CV	1339	1219	1194	1158	1127	1050	776	504	187
Placebo/CV	797	743	706	669	637	595	448	276	84
Placebo/No CV	1355	1231	1195	1151	1119	1041	772	490	188

CV = cardiovascular; CVD = cardiovascular disease; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Primary and Secondary Outcomes by Baseline CVD

	Dapagliflozin 10 mg Events	Placebo Events	Hazard Ratio (95% CI)	p-value Interaction
Primary Outcome: eGFR Decline ≥50% ,ESKD,RenalDeath,orCV Death				
Overall[1]	197/2152	312/2152	0.61 (0.51, 0.72)	
Without CVD[2]	106/1339	175/1355	0.61 (0.48, 0.78)	0.90
With CVD[2]	91/813	137/797	0.61 (0.47, 0.79)	
Secondary Outcome: eGFR Decline ≥50% ,ESKD,orRenalDeath				
Overall[1]	142/2152	243/2152	0.56 (0.45, 0.68)	
Without CVD[2]	93/1339	154/1355	0.61 (0.47, 0.79)	0.29
With CVD[2]	49/813	89/797	0.49 (0.34, 0.69)	
Secondary Outcome: CV Death or hHF				
Overall[1]	100/2152	138/2152	0.71 (0.55, 0.92)	
Without CVD[2]	24/1339	36/1355	0.67 (0.40, 1.13)	0.88
With CVD[2]	76/813	102/797	0.70 (0.52, 0.94)	
Secondary Outcome: All-cause Mortality				
Overall[1]	101/2152	146/2152	0.69 (0.53, 0.88)	
Without CVD[2]	33/1339	53/1355	0.63 (0.41, 0.98)	0.71
With CVD[2]	68/813	93/797	0.70 (0.51, 0.95)	

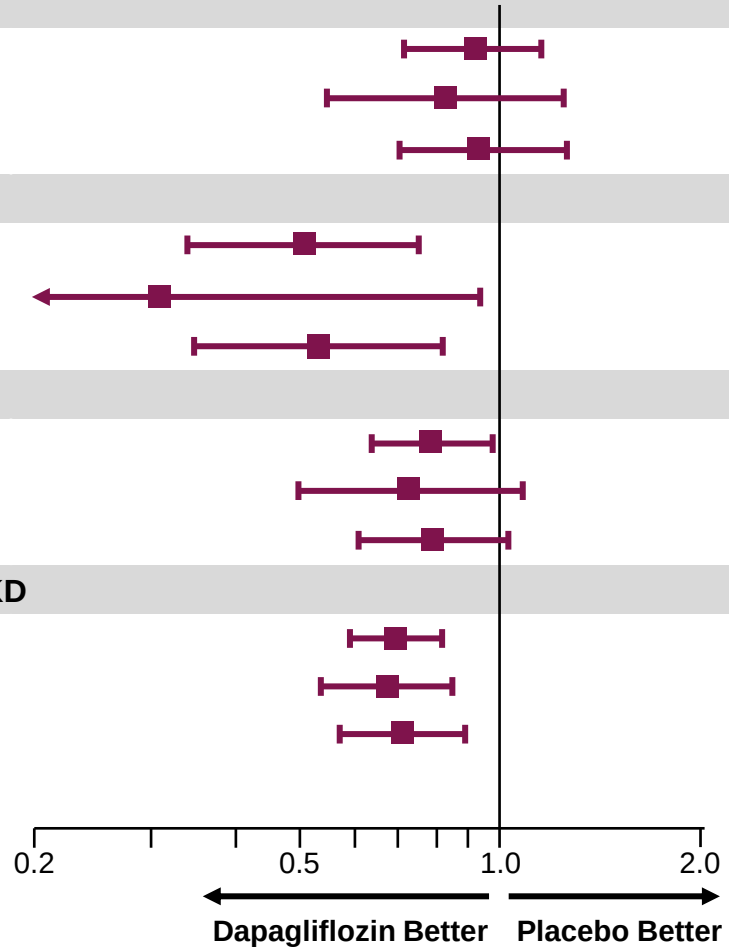


CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure.

1. Heerspink HJL. Et al. *N Engl J Med* 2020;383:1436-1446; 2. McMurray JJV et al. *Circulation*. 2021;143:438–448.

Prespecified and *Post Hoc* Exploratory Outcomes by CV Disease

	Dapagliflozin 10 mg Events	Placebo Events	Hazard Ratio (95% CI)	p-value Interaction
Prespecified Outcome: CV Death, MI, or Stroke				
Overall	132/2152	143/2152	0.92 (0.72, 1.16)	
Without CVD	41/1339	50/1355	0.83 (0.55, 1.25)	0.61
With CVD	91/813	93/797	0.94 (0.71, 1.26)	
Prespecified Outcome: First hHF				
Overall	37/2152	71/2152	0.51 (0.34, 0.76)	
Without CVD	4/1339	13/1355	0.31 (0.10, 0.94)	0.35
With CVD	33/813	58/797	0.54 (0.35, 0.82)	
***Post Hoc* Outcome: CV Death, MI, Stroke, or hHF**				
Overall	158/2152	195/2152	0.79 (0.64, 0.98)	
Without CVD	44/1339	60/1355	0.73 (0.50, 1.08)	0.72
With CVD	114/813	135/797	0.80 (0.62, 1.03)	
***Post Hoc* Outcome: All-cause Mortality, MI, Stroke, hHF, or ESKD**				
Overall	274/2152	376/2152	0.70 (0.60, 0.82)	
Without CVD	118/1339	177/1355	0.68 (0.54, 0.85)	0.77
With CVD	156/813	199/797	0.72 (0.58, 0.89)	



CV = cardiovascular; CVD = cardiovascular disease; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; MI = myocardial infarction.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Safety by Baseline CVD History

		Dapagliflozin 10 mg No CVD n = 1337 CVD n = 812 Number (%)	Placebo No CVD n = 1352 CVD n = 797 Number (%)	P value for interaction
Any serious AE	No CVD	287 (21.5)	371 (27.4)	0.09
	CVD	346 (42.6)	358 (44.9)	
AE leading to study drug discontinuation	No CVD	73 (5.5)	70 (5.2)	0.36
	CVD	45 (5.5)	53 (6.6)	
Amputation	No CVD	10 (0.7)	15 (1.1)	0.40
	CVD	25 (3.1)	24 (3.0)	
Fracture	No CVD	44 (3.3)	44 (3.3)	0.15
	CVD	41 (5.0)	25 (3.1)	
Renal adverse event	No CVD	76 (5.7)	99 (7.3)	0.61
	CVD	79 (9.7)	89 (11.2)	
Volume depletion	No CVD	75 (5.6)	46 (3.4)	0.20
	CVD	52 (6.4)	44 (5.5)	
Major hypoglycemia[a]	No CVD	3 (0.2)	13 (1.0)	0.12
	CVD	11 (1.4)	15 (1.9)	

Definite or probable ketoacidosis occurred in 2 patients without CV disease randomly allocated to placebo; there were no cases of ketoacidosis in the dapagliflozin group.

[a]The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

AE = adverse event; CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Summary

- In this analysis, dapagliflozin reduced the risk of kidney failure, death from CV causes or hHF, and prolonged survival, in people with chronic kidney disease, independent of the presence of concomitant CVD
- Dapagliflozin was well tolerated; the safety profile was consistent between treatment groups when stratified by baseline CVD history

CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; hHF = hospitalization for heart failure.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

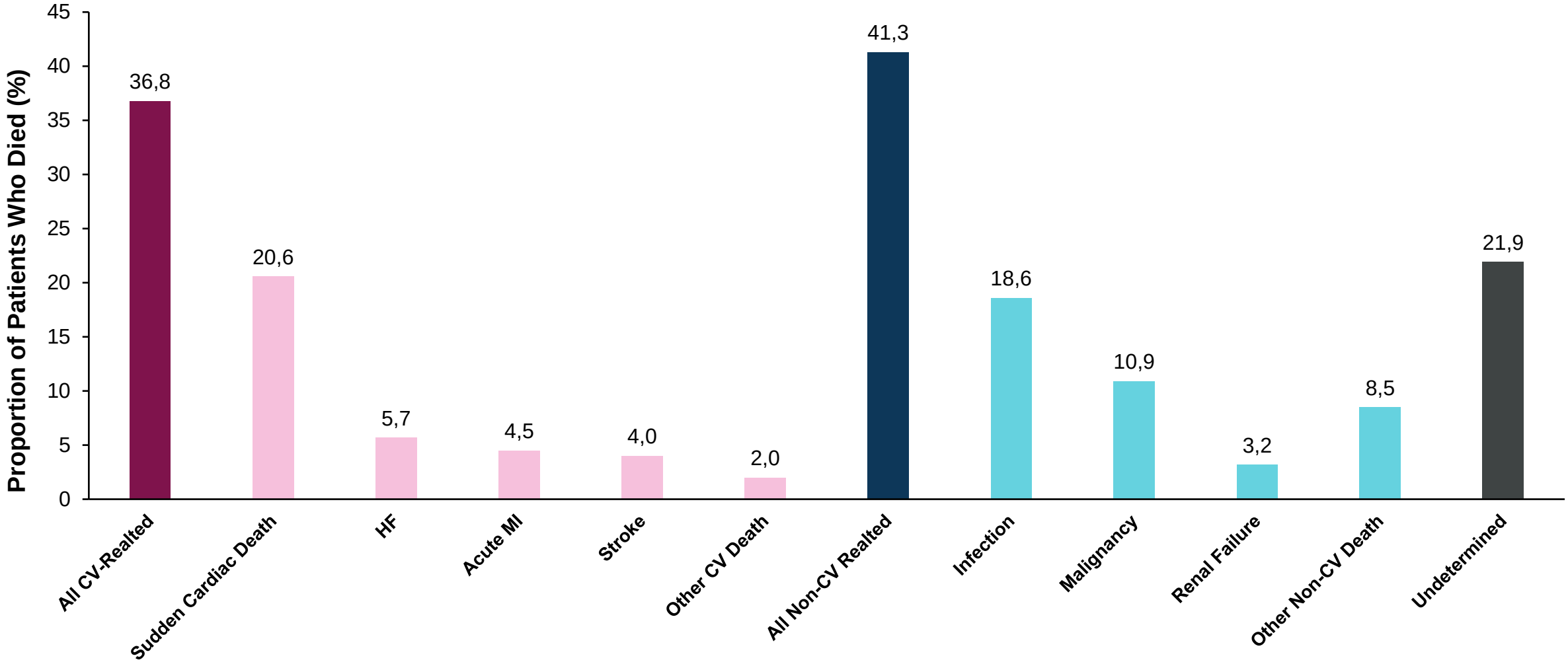
DAPA-CKD Subgroup Analysis
Causes of Mortality

A secondary analysis assessed the causes of death in DAPA-CKD patients, and assessed the effects of dapagliflozin on CV and non-CV causes of death in these patients

CV=cardiovascular.

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

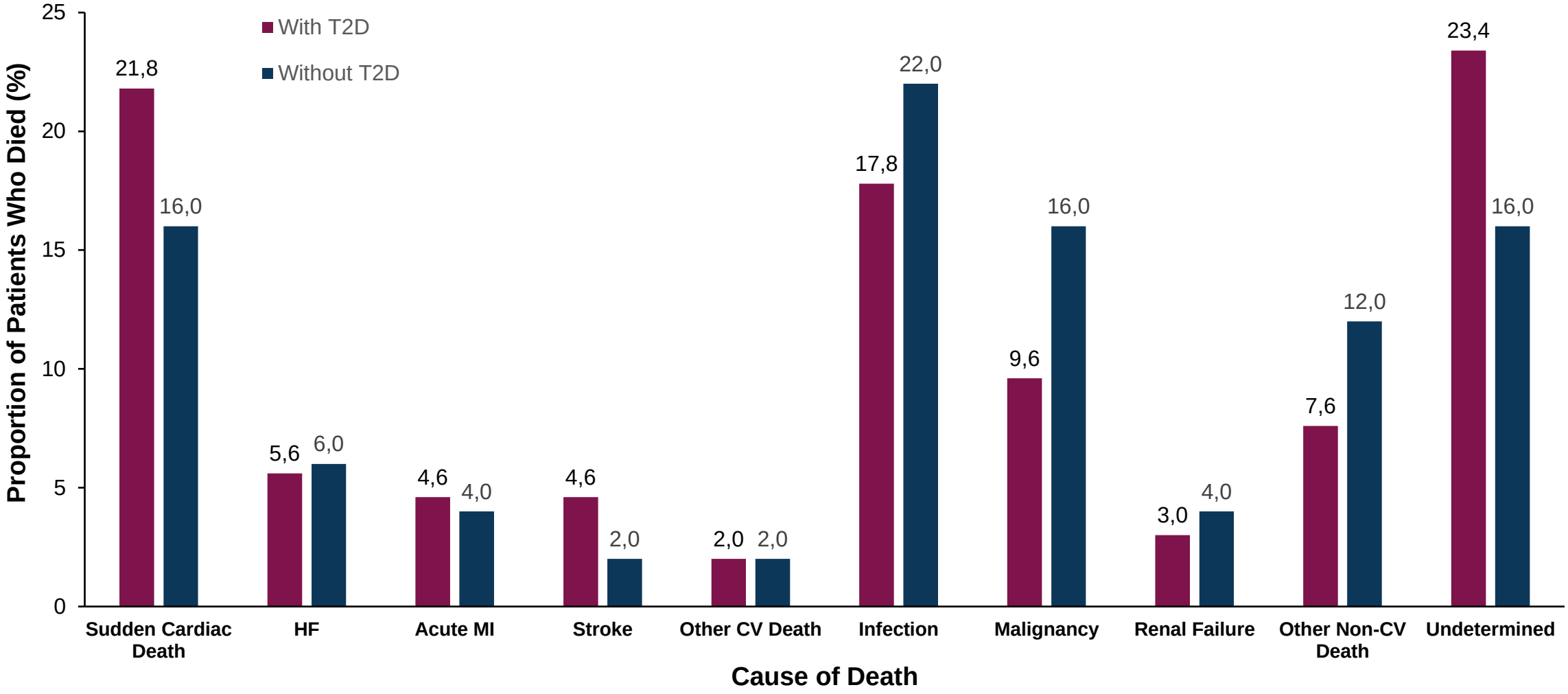
Main Causes of Death in DAPA-CKD



CV = cardiovascular; HF = heart failure; MI = myocardial infarction.

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

Main Causes of Death in DAPA-CKD by T2D Status

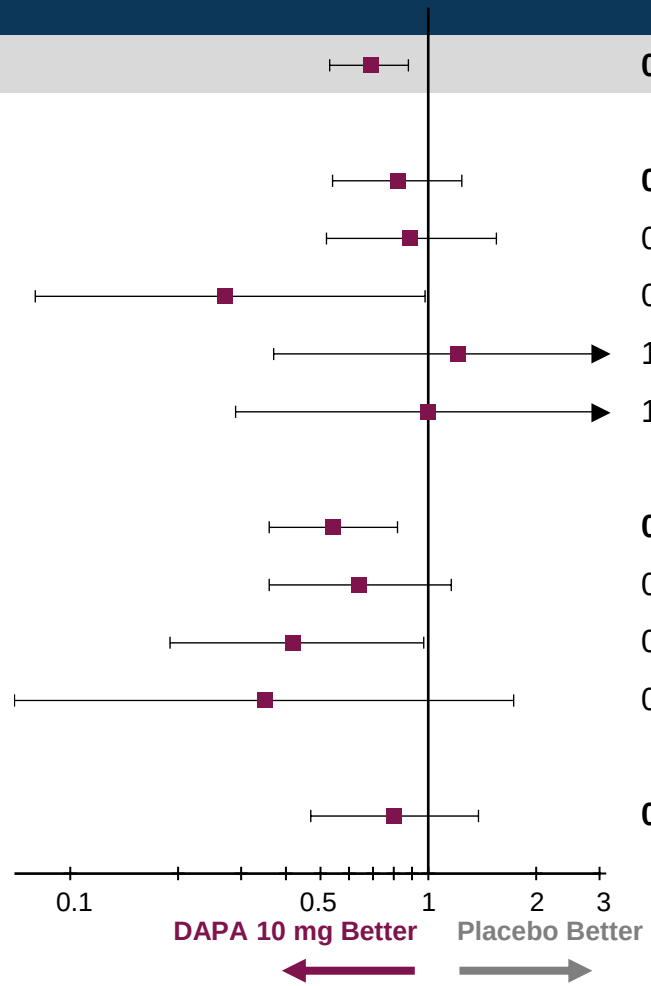


CV = cardiovascular; HF = heart failure; MI = myocardial infarction; T2D = type 2 diabetes.

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

Effect of Dapagliflozin on CV Death and Non-CV Death

	Dapagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)	P Value
	No. of patients/total no.			
All-cause mortality	**101/2152**	**146/2152**	**0.69 (0.53, 0.88)**	**0.003**
CV death	**41/2152**	**50/2152**	**0.82 (0.54, 1.24)**	**0.338**
Sudden cardiac death	24/2152	27/2152	0.89 (0.52, 1.55)	
Heart failure	3/2152	11/2152	0.27 (0.08, 0.98)	
Acute MI	6/2152	5/2152	1.21 (0.37, 3.96)	
Stroke	5/2152	5/2152	1.00 (0.29, 3.74)	
Non-CV death	**36/2152**	**66/2152**	**0.54 (0.36, 0.82)**	**0.003**
Infection	18/2152	28/2152	0.64 (0.36, 1.16)	
Malignancy	8/2152	19/2152	0.42 (0.19, 0.97)	
Renal failure	2/2152	6/2152	0.35 (0.07, 1.73)	
Undetermined	**24/2152**	**30/2152**	**0.80 (0.47, 1.38)**	**0.426**



CV = cardiovascular; DAPA= dapagliflozin; MI = myocardial infarction; No. = number.

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

All-Cause Mortality in Patients Who Did and Did Not Reach Chronic Dialysis

	Dapagliflozin		Placebo		Total	
	n (%)	Event rate (100 pt-yrs)	n (%)	Event rate (100 pt-yrs)	n (%)	Event rate (100 pt-yrs)
Overall mortality	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	247/4304 (5.7)	2.6
Without chronic dialysis, n	2084		2053		4137	
All-cause mortality	89 (4.3)	1.9	121 (5.9)	2.6	210 (5.1)	2.2
With chronic dialysis, n	68		99		167	
All-cause mortality	12 (17.6)	8.6	25 (25.3)	13.4	37 (22.2)	11.4

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

Summary

- The benefits of dapagliflozin on overall mortality included reductions in both CV related death and non-CV related death
- The incidence of CV death and non-CV death was generally similar (36.8% vs 41.3%, respectively)
- The most common causes of CV mortality were sudden cardiac death and heart failure
- The most common causes of non-CV mortality were infection and malignancy
- The reduction in all-cause mortality seen with dapagliflozin was consistent in patients requiring dialysis and in those without dialysis

CV = cardiovascular.

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

DAPA-CKD Subgroup Analysis
Baseline Diuretic and MRA Use

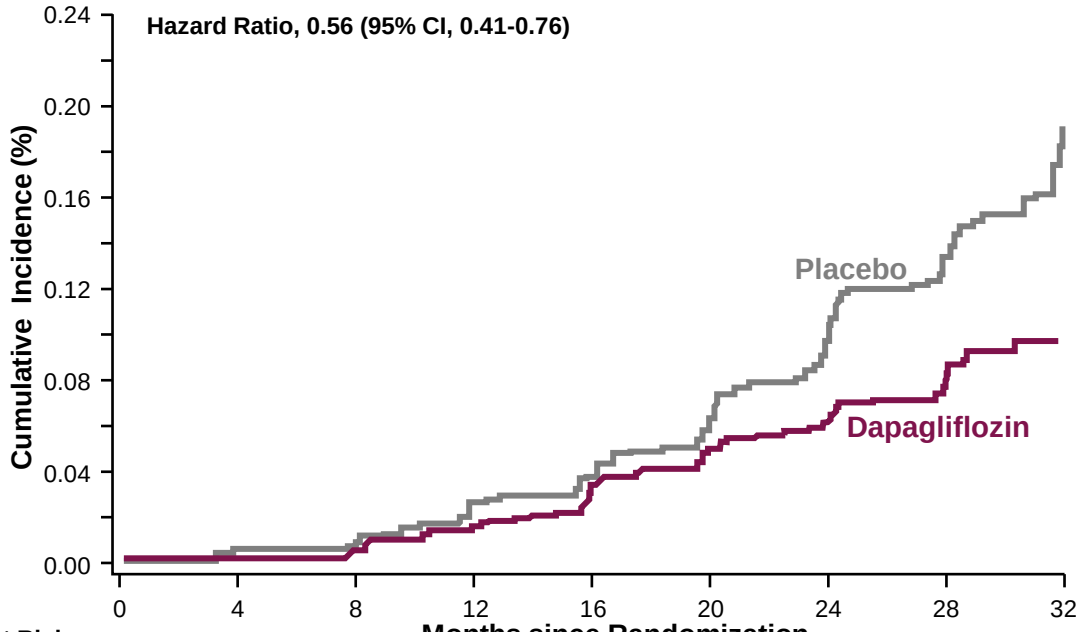
In a secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to baseline diuretic and MRA use

MRA=mineralocorticoid receptor antagonists.

Heerspink HL. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

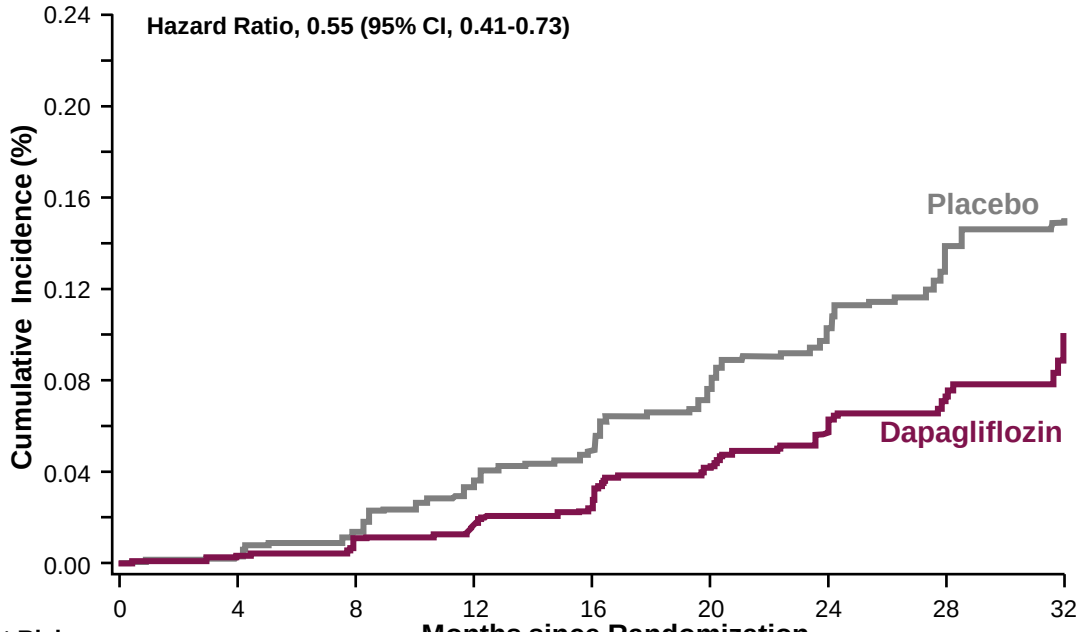
Renal Composite Outcome[a] in Patients With and Without Diuretic Use at Baseline

With Diuretic Use



No at Risk									
Dapagliflozin	928	897	876	854	826	765	593	375	150
Placebo	954	906	880	847	818	757	587	358	125

Without Diuretic Use



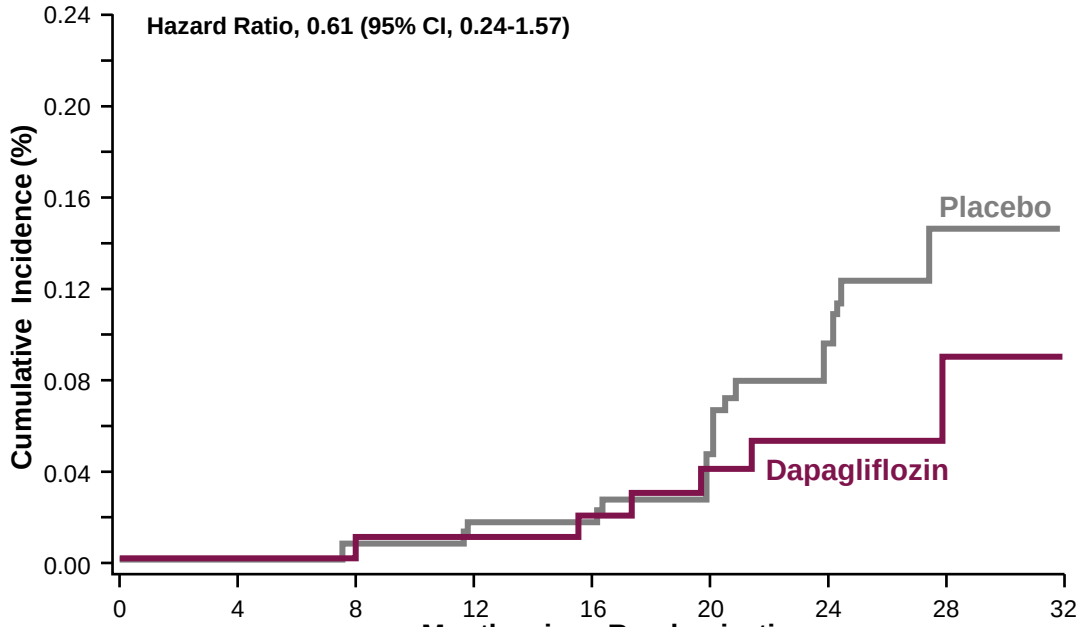
No at Risk									
Dapagliflozin	1224	1104	1079	1044	1015	936	695	456	159
Placebo	1198	1087	1056	1011	973	907	645	416	145

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

Heerspink HL. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

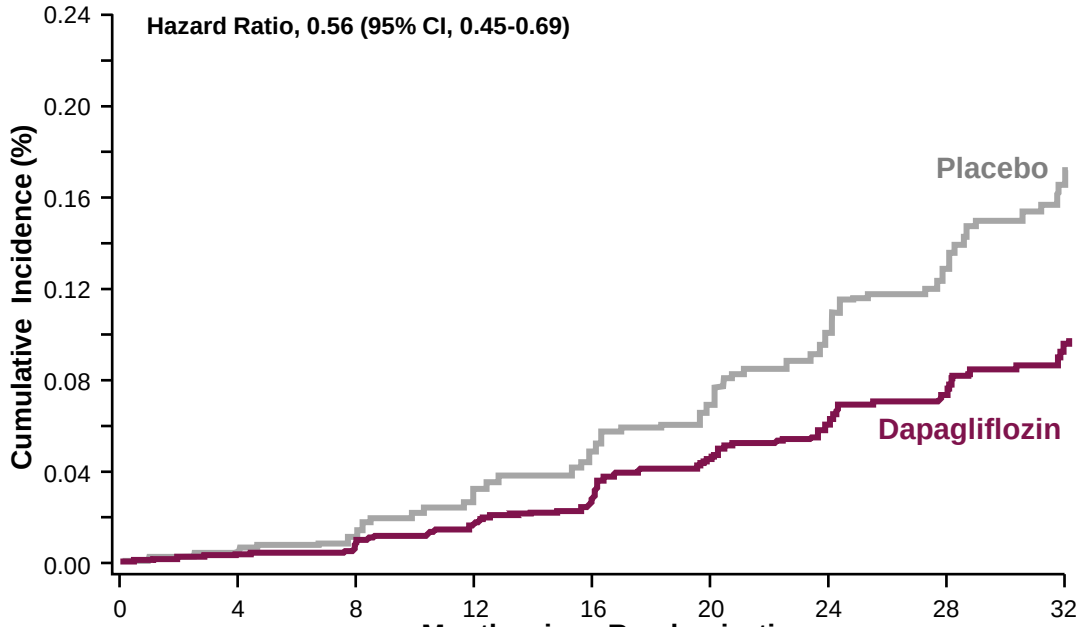
Renal Composite Outcome[a] in Patients With and Without MRA Use at Baseline

With MRA Use



No at Risk									
Dapagliflozin	109	107	105	102	100	88	71	51	22
Placebo	120	117	112	110	106	96	65	36	16

Without MRA Use



No at Risk									
Dapagliflozin	2043	1894	1850	1796	1741	1613	1217	780	287
Placebo	2032	1876	1824	1748	1685	1568	1167	780	254

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

MRA = mineralocorticoid receptor antagonist.

Heerspink HL. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

Safety by Diuretic Use at Baseline

Safety by Diuretic Use at Baseline

Safety outcomes, n (%)	With diuretic use		Without diuretic use	
	Dapagliflozin 10 mg (n=927)	Placebo (n=953)	Dapagliflozin 10 mg (n=1222)	Placebo (n=1196)
Discontinuation due to adverse event	6.0	6.0	5.1	5.5
Any serious adverse event[a]	33.4	38.2	23.2	25.9

Safety by MRA Use at Baseline

Safety outcomes, n (%)	With MRA use		Without MRA use	
	Dapagliflozin (n=109)	Placebo (n=120)	Dapagliflozin (n=2040)	Placebo (n=2029)
Discontinuation due to adverse event	3.7	5.0	5.6	5.8
Any serious adverse event[a]	39.4	42.5	27.0	30.7

[a]Includes death.

MRA = mineralocorticoid receptor antagonist.

Heerspink HL. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

Summary

- In this analysis, renal composite outcome (sustained ≥50% eGFR decline, ESKD, renal death) benefit with dapagliflozin was seen regardless of baseline diuretic and MRA use
- Dapagliflozin was well tolerated; the safety profile was consistent between treatment groups when stratified by baseline diuretic and MRA use

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; MRA = mineralocorticoid receptor antagonist.

Heerspink HL. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

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 ACEiorARB	Canagliflozin vs Placebo ≥4 weeks stable on ACEiorARB	Empagliflozin vs Placebo On ACEi or ARB	Finerenone vs Placebo ≥4 weeks on ACEiorARB
Patient Population	• T2D and non-DM • eGFR ≥25 to ≤75 mL/min/1.73m^2 • UACR ≥200 to ≤5000 mg/g	• T2D • eGFR ≥30 to <90 mL/min/1.73m^2 • UACR >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 ≥200 mg/g	• T2D • eGFR ≥25 to <60 mL/min/1.73m^2 and UACR ≥ 30 to <300 mg/g and presence of diabetic retinopathy **or** eGFR ≥25 to <75 mL/min/1.73m^2 and UACR ≥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.