Late-breaking Presentation on Key Kidney Outcomes

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VERTIS

e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

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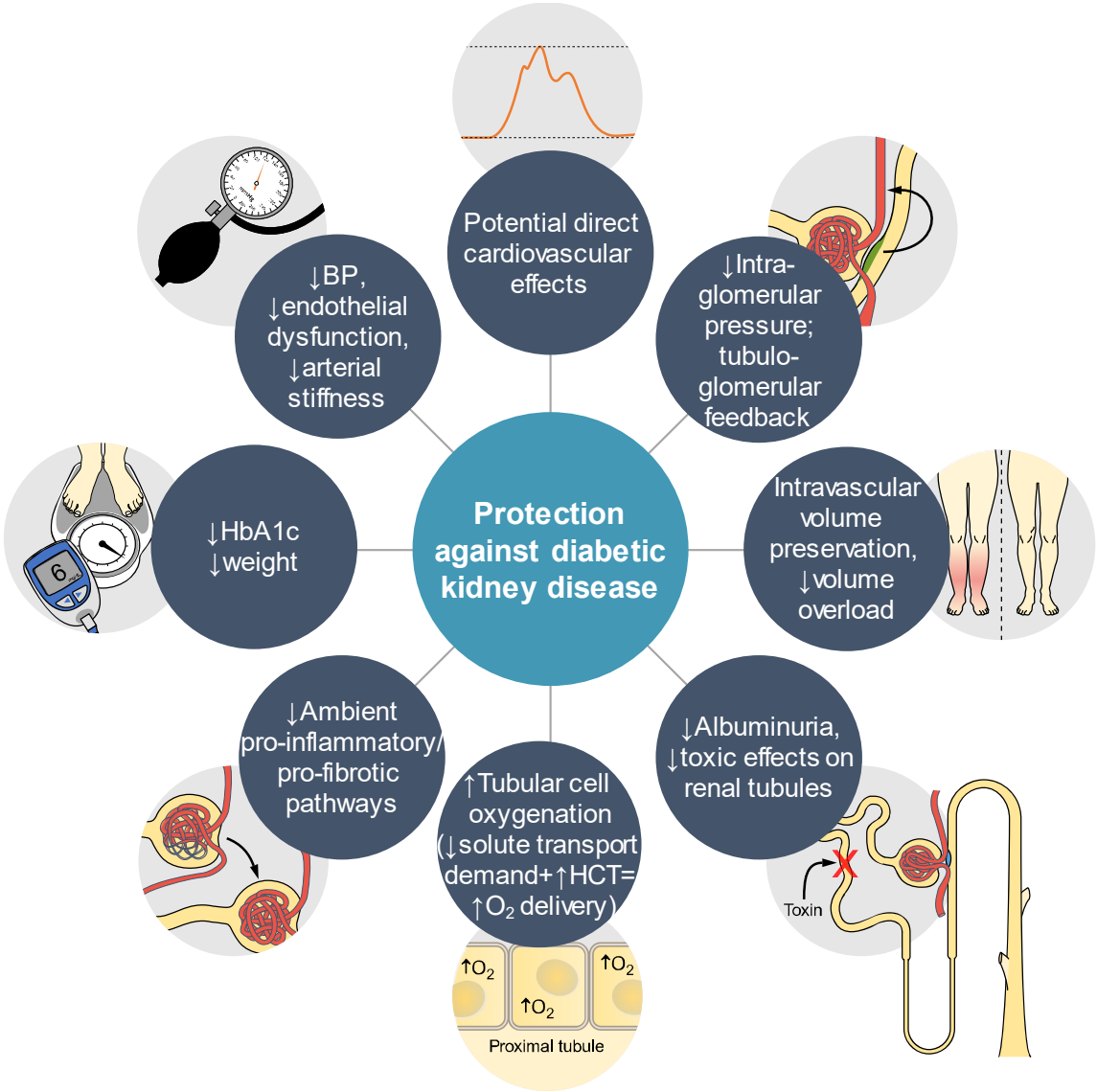
Proposed renal protective pathways with SGLT2 inhibitors



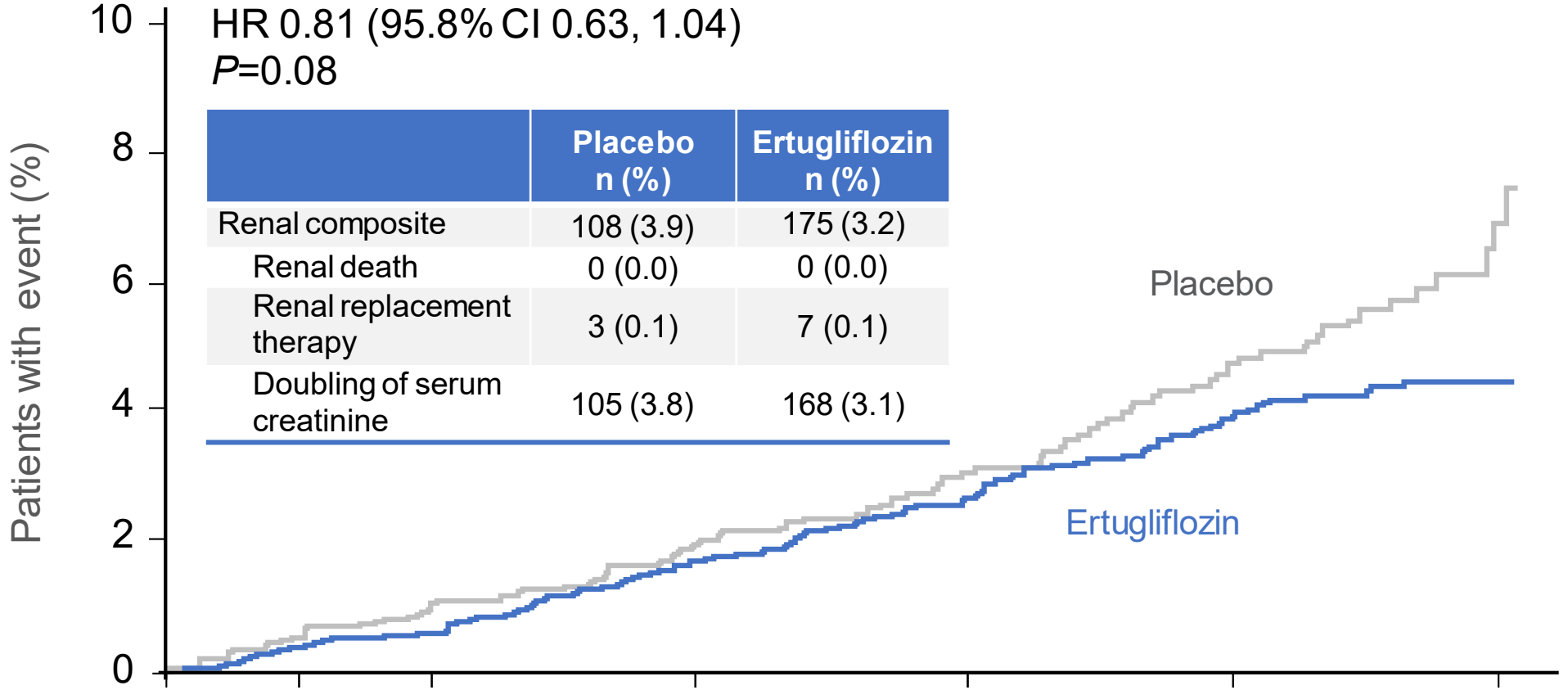
BP, blood pressure; CKD, chronic kidney disease; HbA1c, glycated haemoglobin; HCT, haematocrit; SGLT2, sodium-glucose cotransporter 2.
Reproduced from *Kidney International*, 94(1), Hiddo J.L. Heerspink, Mikhail Kosiborod, Silvio E. Inzucchi, David Z.I. Cherney. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors, 26–39, Copyright (2018), with permission from Elsevier.

Renal composite†[1]

Renal death, dialysis/transplant or doubling of serum creatinine

HR 0.81 (95.8% CI 0.63, 1.04)
P=0.08

	Placebo n (%)	Ertugliflozin n (%)
Renal composite	108 (3.9)	175 (3.2)
Renal death	0 (0.0)	0 (0.0)
Renal replacement therapy	3 (0.1)	7 (0.1)
Doubling of serum creatinine	105 (3.8)	168 (3.1)



No. at risk							
Placebo	2747	2703	2643	2543	1371	1116	215
All ertugliflozin	5499	5394	5299	5110	2756	2272	406

†Intention-to-treat analysis set that included all randomised patients with no upper limit on the ascertainment window for the superiority outcomes (n=5499 for ertugliflozin and n=2747 for placebo). CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol. CI, confidence interval; HR, hazard ratio. [1]Cannon CP. Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial – VERTIS CV. American Diabetes Association Virtual Scientific Sessions. 2020.

Pre-specified exploratory kidney endpoints

- Cox proportional hazard of composite kidney outcomes
  - Sustained doubling of serum creatinine, chronic kidney dialysis/transplant or renal death
  - **Sustained 40% decrease in eGFR**, or chronic kidney dialysis/transplant or renal death
  - All in the overall population and by baseline kidney function categories

- Cox proportional hazard for categorical changes in albuminuria
  - **Progression** of albuminuria
  - **Regression** of albuminuria
  - In overall population and by baseline kidney function categories

- UACR over time
  - Changes over time in the geometric mean for UACR
  - In overall population and by baseline albuminuria status

- eGFR over time
  - Changes over time in eGFR calculated by the CKD-EPI formula
  - In overall population and by baseline albuminuria status

ARF, acute renal failure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

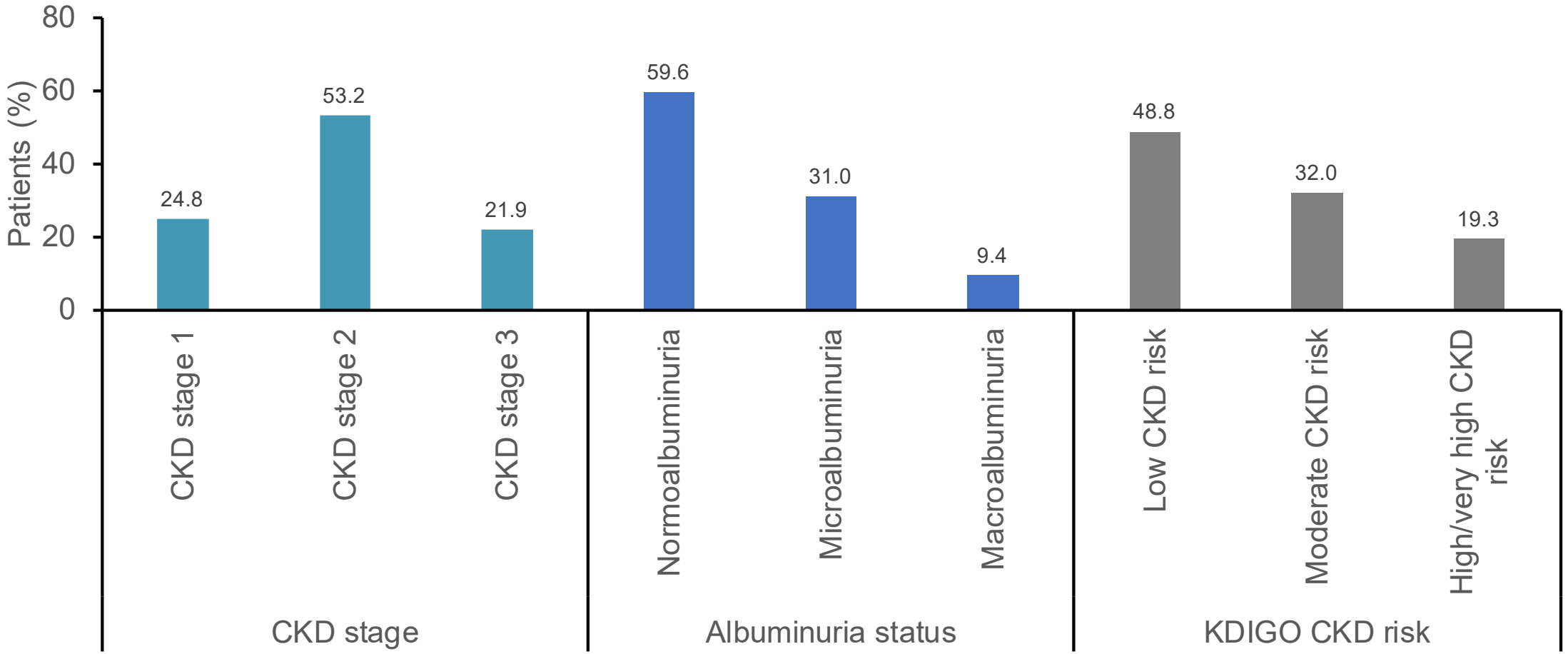
Classification by baseline kidney categories

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR, mL min^{-1} 1.73 m^{-2} Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	Low risk	Moderate Risk	High risk
	G2	Mildly decreased	60–89	Low risk	Moderate risk	High risk
	G3a	Mildly to moderately decreased	45–59	Moderate risk	High risk	Very high risk
	G3b	Moderately to severely decrease	30–44	High risk	Very high risk	Very high risk
	G4	Severely decreased	15–29	Patients with eGFR <30 mL min^{-1} 1.73 m^{-2} excluded from VERTIS CV		
	G5	Kidney failure	<15			

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. Reprinted from *Kidney International*, 80(1), Andrew S. Levey, Paul E. de Jong, Josef Coresh, Meguid E.I. Nahas, Brad C. Astor, Kunihiro Matsushita, Ron T. Gansevoort, Bertram L. Kasiske, Kai-Uwe Eckardt. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report, 17–28, Copyright (2011), with permission from Elsevier.

Distribution by baseline kidney categories (overall population)



- Baseline kidney subgroups were generally balanced between the placebo and ertugliflozin groups

CKD, chronic kidney disease; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease.

Pre-specified and exploratory secondary analyses

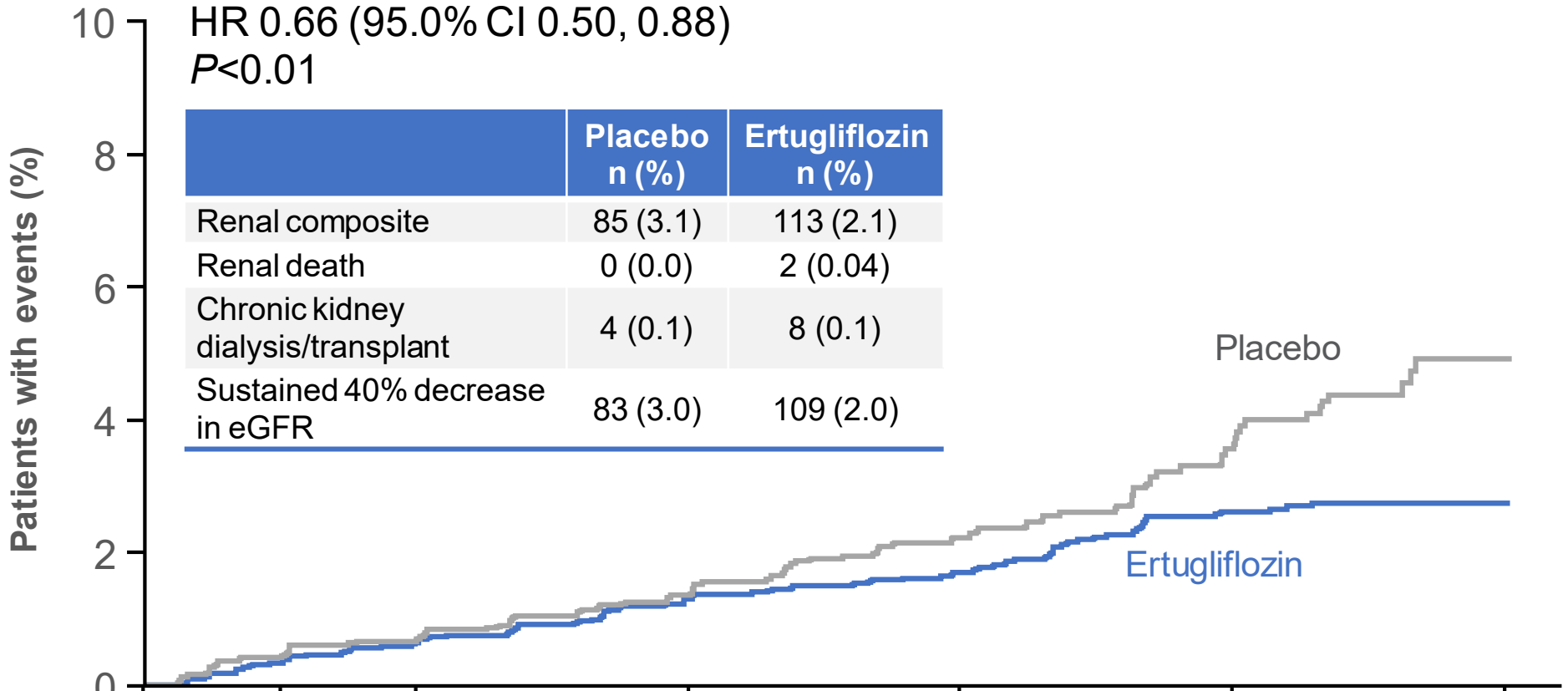
	Placebo N=2747		Ertugliflozin N=5499			
	n (%)	Event rate 100 P-Y	n (%)	Event rate 100 P-Y	HR (95% CI)	*P* value
Doubling of serum creatinine, kidney dialysis/transplant or renal death[1]	108 (3.93)	1.15	175 (3.18)	0.93	0.81 (0.63, 1.04)	0.081
Sustained doubling of serum creatinine, chronic kidney dialysis/transplant or renal death	33 (1.20)	0.35	43 (0.78)	0.23	0.65 (0.41, 1.02)	0.062
Sustained 40% reduction in eGFR, chronic kidney dialysis/transplant or renal death	85 (3.09)	0.90	113 (2.05)	0.60	0.66 (0.50, 0.88)	<0.01

eGFR calculated by the Modification of Diet in Renal Disease formula.
AERR, absolute event rate reduction; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; P-Y, person-years. [1]Cannon CP. Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial - VERTIS CV. American Diabetes Association Virtual Scientific Sessions. 2020.

Exploratory renal composite: *Sustained 40% decrease from baseline in eGFR*, chronic kidney dialysis/transplant or renal death†

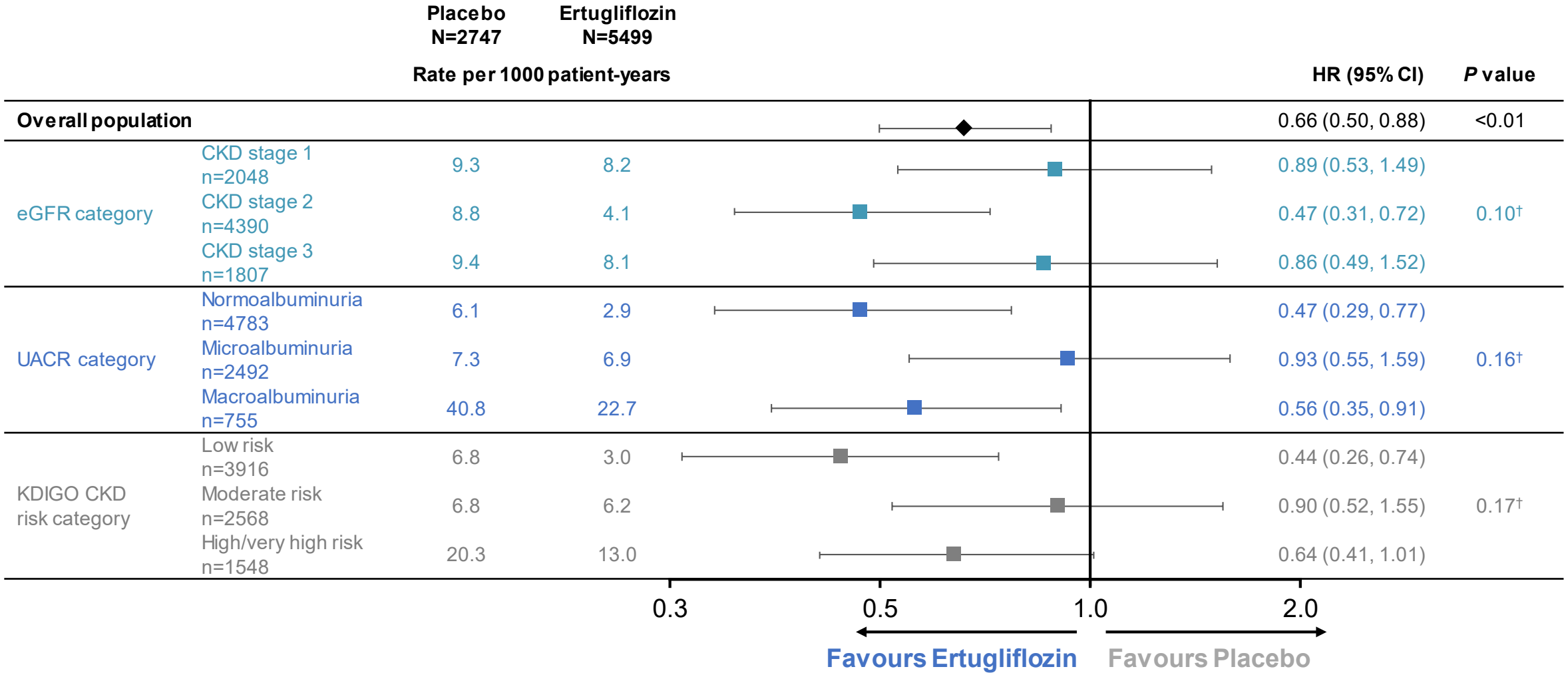
HR 0.66 (95.0% CI 0.50, 0.88)
P<0.01

	Placebo n (%)	Ertugliflozin n (%)
Renal composite	85 (3.1)	113 (2.1)
Renal death	0 (0.0)	2 (0.04)
Chronic kidney dialysis/transplant	4 (0.1)	8 (0.1)
Sustained 40% decrease in eGFR	83 (3.0)	109 (2.0)



†Intention-to-treat analysis set that included all randomised patients.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

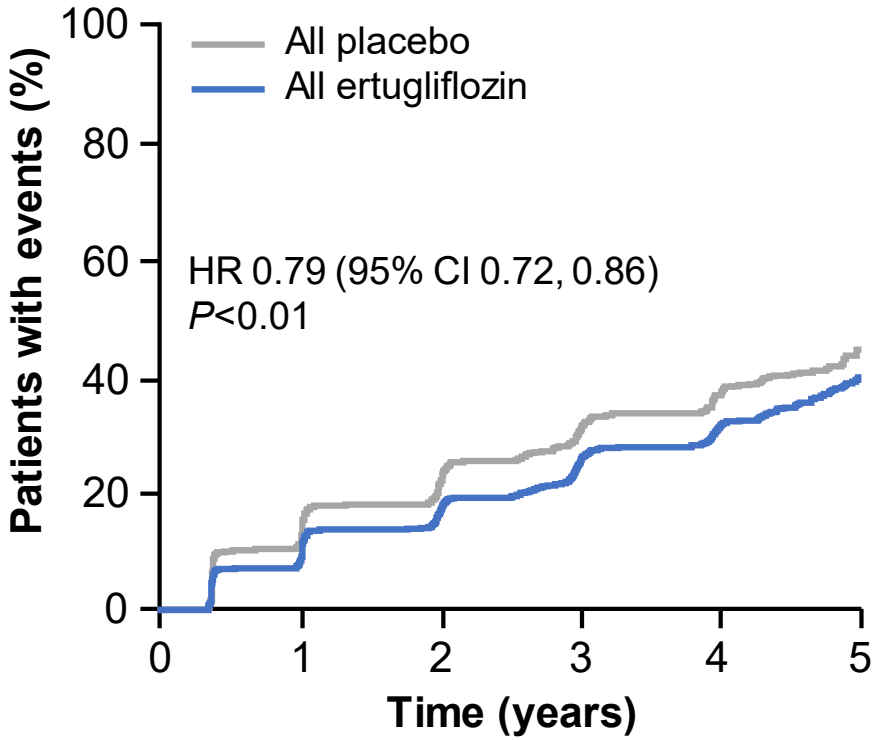
Composite of sustained 40% decrease in eGFR, or chronic kidney dialysis/transplant or renal death by baseline kidney function categories



†The interaction *P* value is for the treatment-by-subgroup interaction.
CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease; UACR, urinary albumin-to-creatinine ratio

Ertugliflozin reduces the risk for progression of albuminuria in the overall cohort

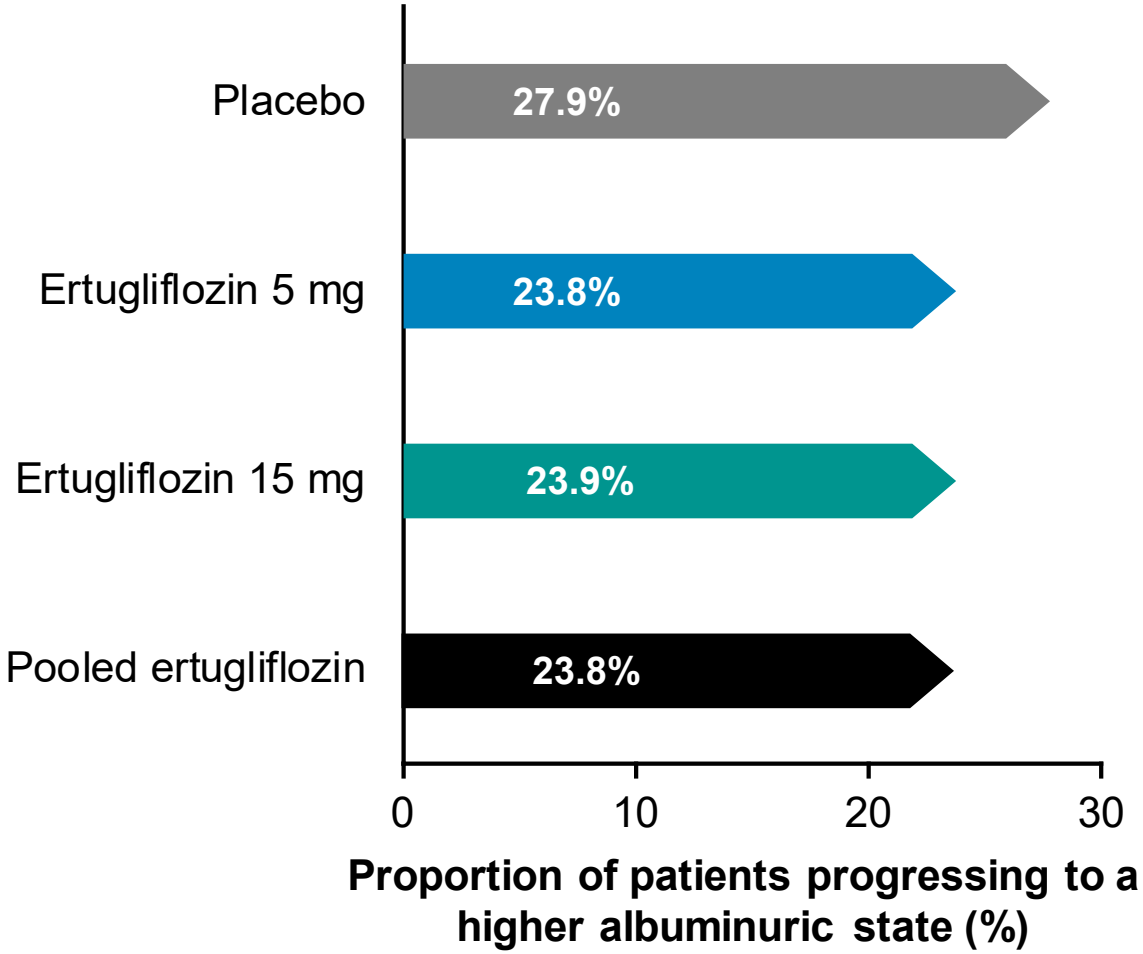
Kaplan–Meier curves of time to first progression of albuminuria†



Number of patients at risk

All placebo	2745	2006	1633	713	520	62
All ertugliflozin	5493	4245	3632	1647	1251	162

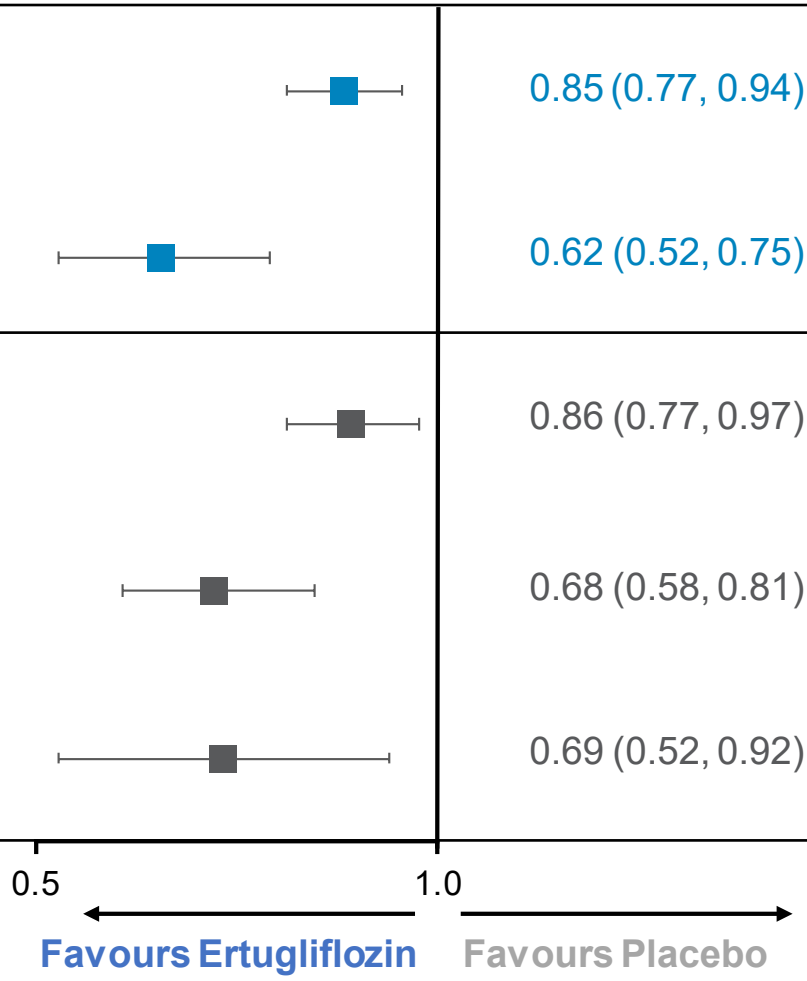
Progression to a higher albuminuric state



†Intention-to-treat analysis set that included all randomised patients.
CI, confidence interval; HR, hazard ratio.

Progression of CKD by baseline kidney function category

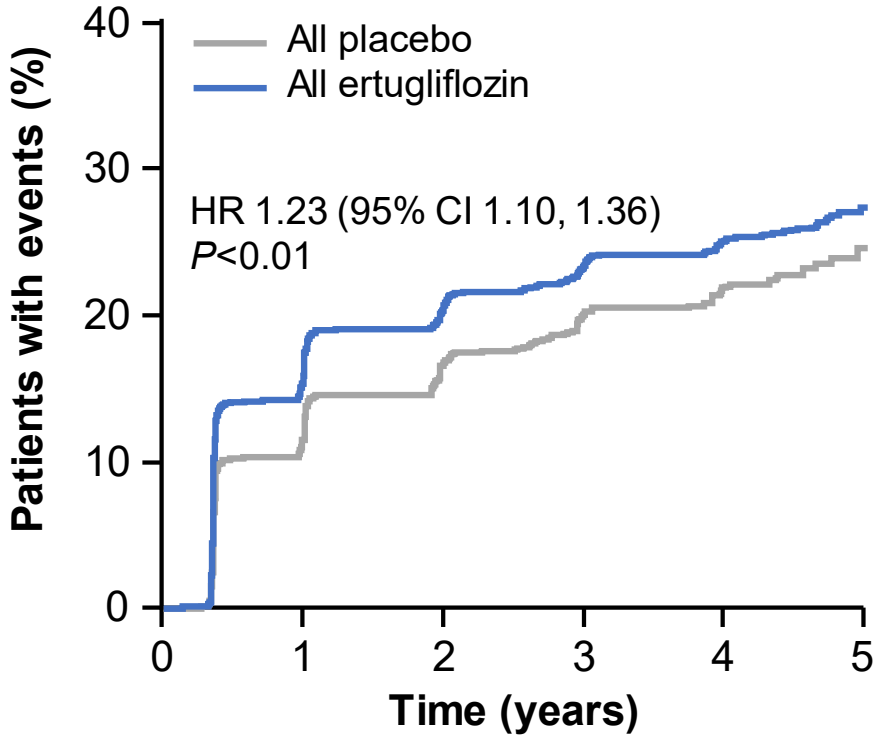
		Placebo N=2747	Ertugliflozin N=5499	HR (95% CI)	*P* value for interaction
		Rate per 1000 patient-years			
UACR category	Normoalbuminuria n=4783	162.6	137.4	0.85 (0.77, 0.94)	0.02
	Microalbuminuria n=2492	95.1	58.8	0.62 (0.52, 0.75)	
KDIGO CKD risk category	Low risk n=3916	151.2	130.1	0.86 (0.77, 0.97)	
	Moderate risk n=2568	116.0	78.7	0.68 (0.58, 0.81)	0.05
	High/very high risk n=1548	69.9	48.2	0.69 (0.52, 0.92)	



CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease; UACR, urinary albumin-to-creatinine ratio.

Ertugliflozin improves the chances for regression of albuminuria in the overall cohort

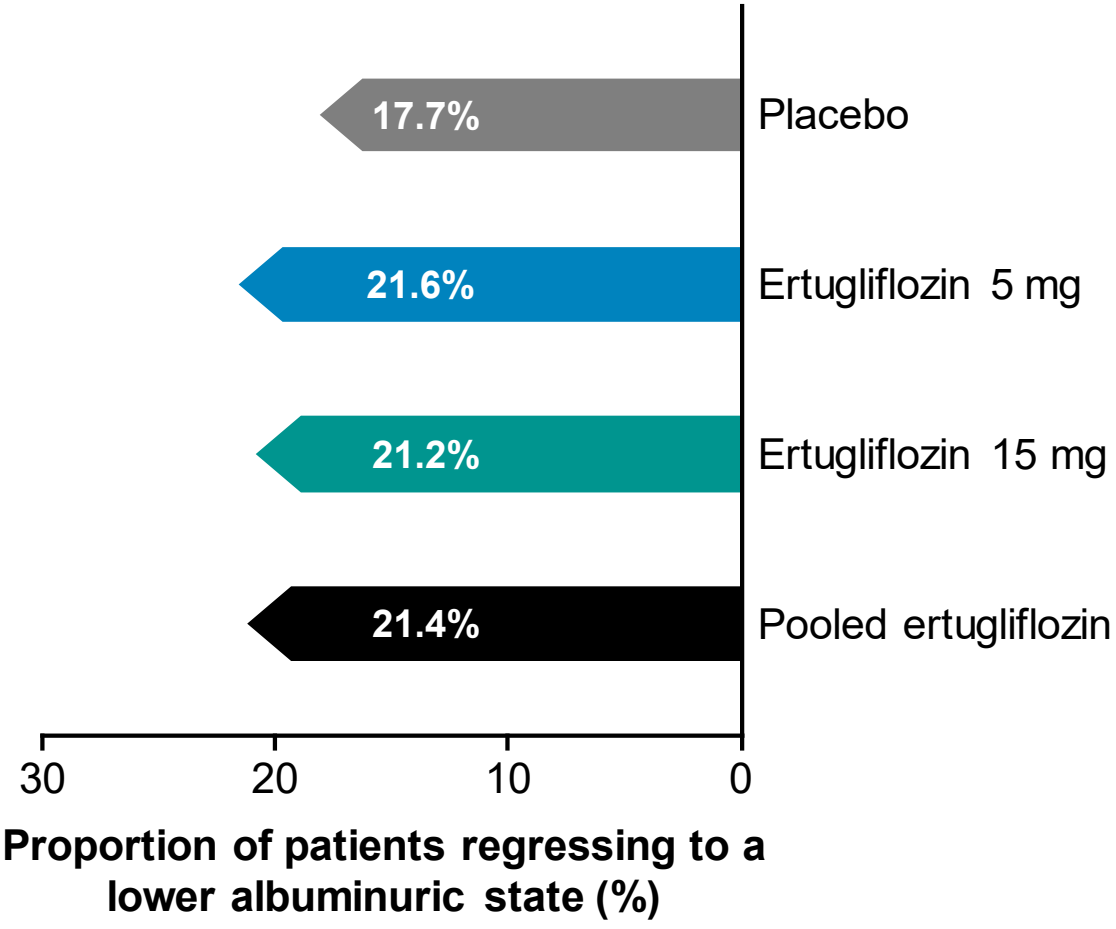
Kaplan–Meier curves of time to first regression of albuminuria†



Number of patients at risk

All placebo	2745	2050	1747	812	631	85
All ertugliflozin	5493	3972	3491	1658	1323	174

Progression to a lower albuminuric state



†Intention-to-treat analysis set that included all randomised patients.
CI, confidence interval; HR, hazard ratio.

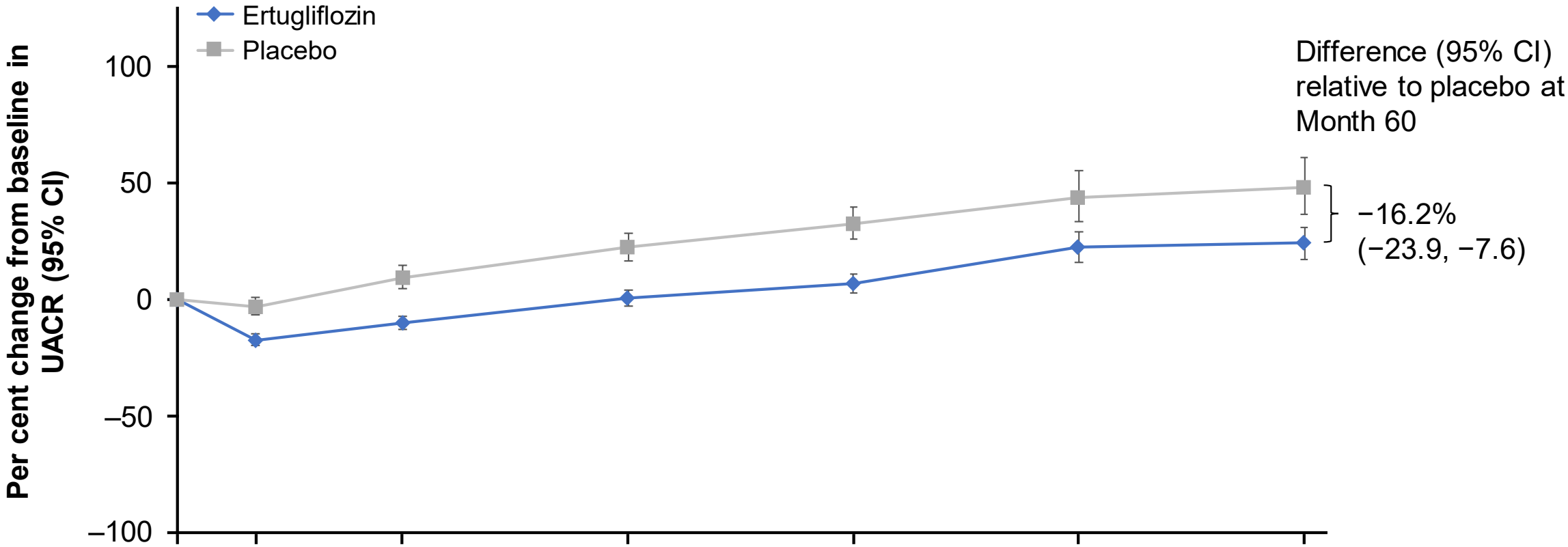
Regression of CKD by baseline kidney function category

		Placebo N=2747	Ertugliflozin N=5499	HR (95% CI)	*P* value for interaction
		Rate per 1000 patient-years			
UACR category	Microalbuminuria n=2492	253.2	311.0	1.24 (1.10, 1.39)	0.04
	Macroalbuminuria n=755	239.2	439.7	1.71 (1.37, 2.15)	
KDIGO CKD risk category	Moderate risk n=2568	165.3	202.3	1.24 (1.08, 1.42)	0.61
	High/very high risk n=1548	204.4	288.1	1.38 (1.17, 1.63)	

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio;
KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease;
UACR, urinary albumin-to-creatinine ratio.

Mean per cent change in UACR (geometric mean) over time†

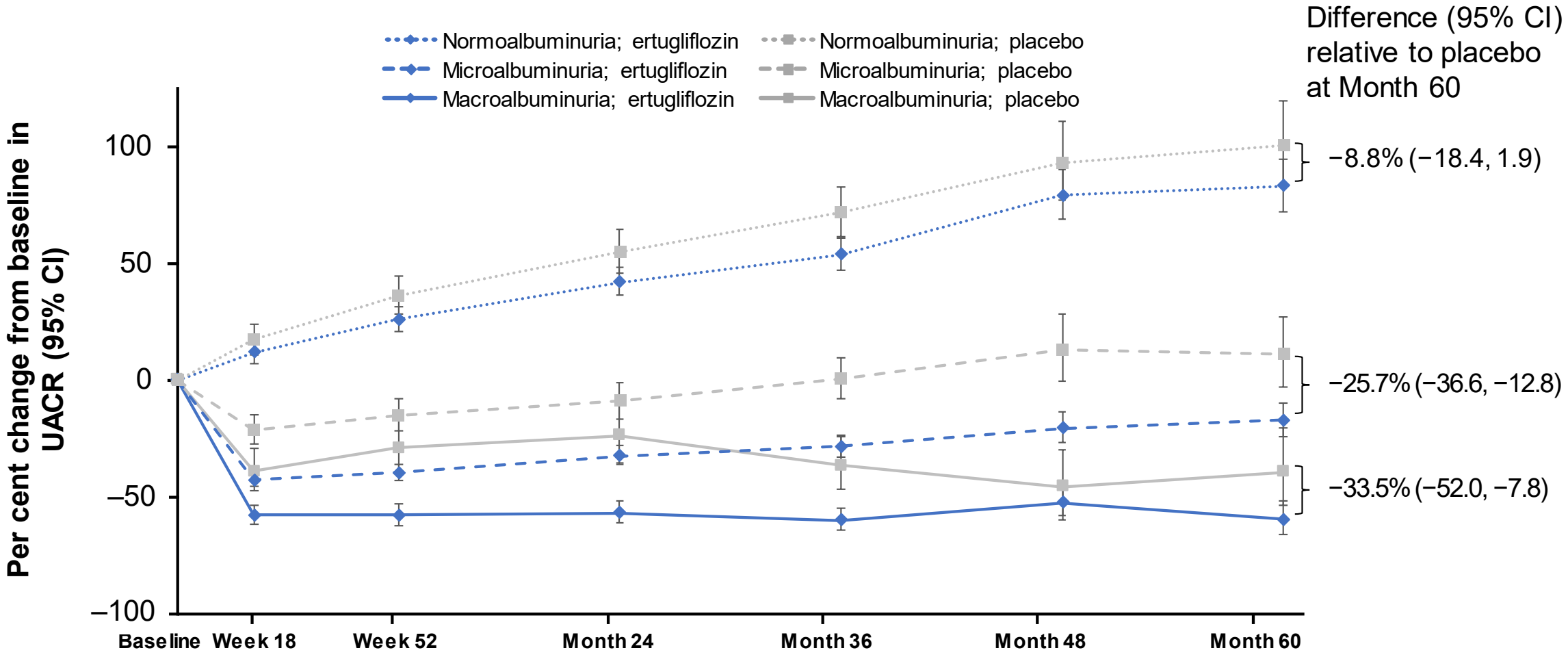
Overall population



Patients, n	Baseline	Week 18	Week 52	Month 24	Month 36	Month 48	Month 60
Placebo	2684	2536	2309	2071	1886	769	715
Ertugliflozin	5346	5063	4709	4317	3942	1703	1590

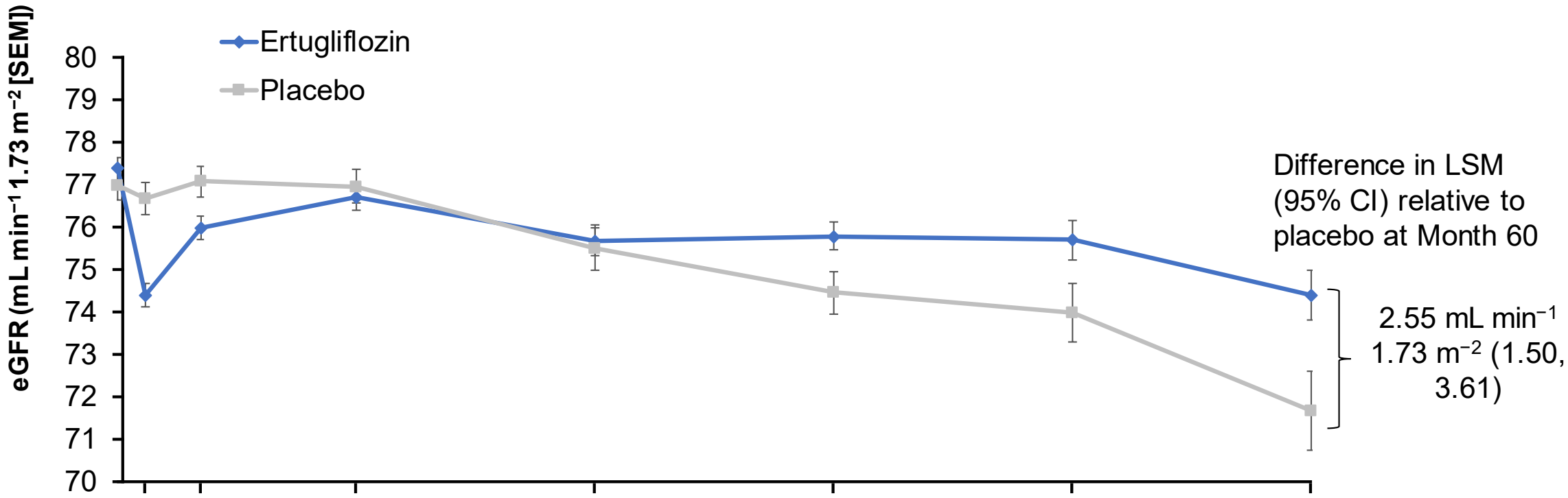
†Full analysis set included all randomised participants who received one or more doses of blinded study medication and had one or more measurements of the analysis endpoint.
CI, confidence interval; UACR, urinary albumin-to-creatinine ratio.

Mean per cent change from baseline in UACR (geometric mean) over time by UACR category†



†Full analysis set included all randomised participants who received one or more doses of blinded study medication and had one or more measurements of the analysis endpoint.
CI, confidence interval; UACR, urinary albumin-to-creatinine ratio.

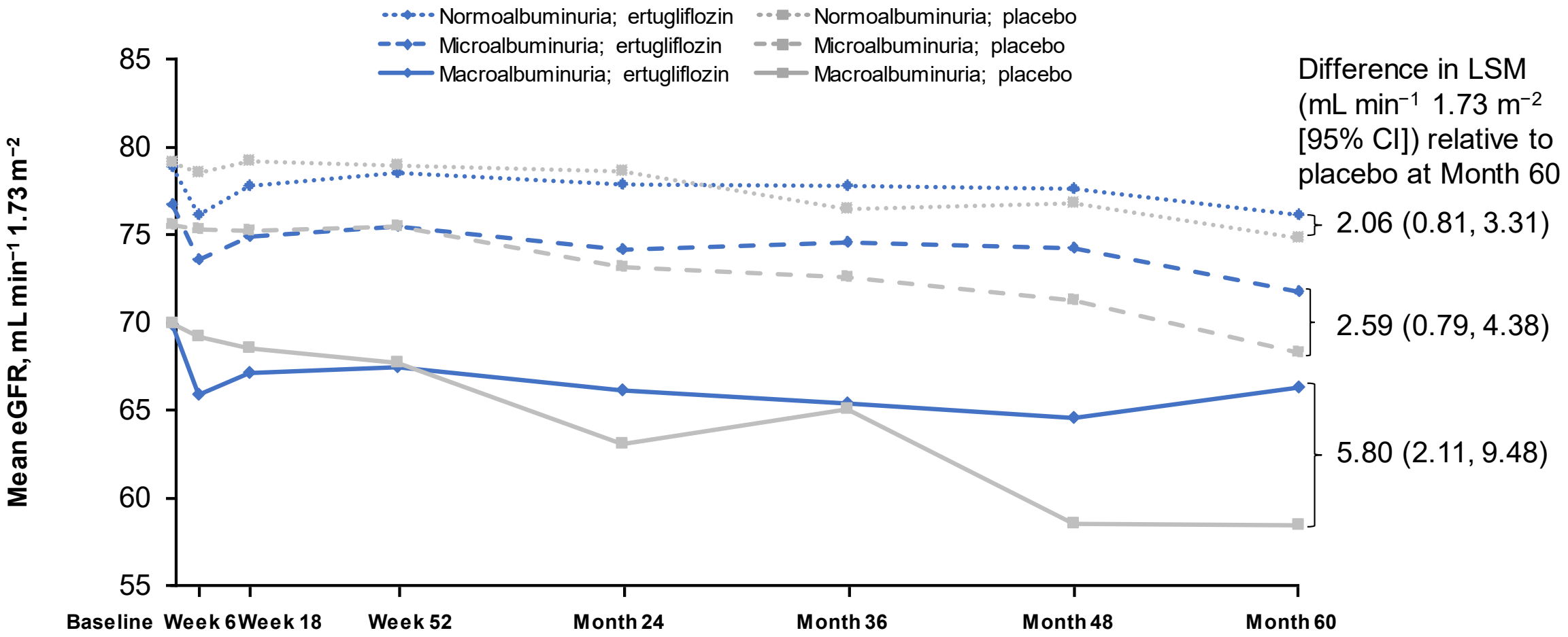
VERTIS CV: Mean eGFR over time†
Overall population



Patients, n	Baseline	Week 6	Week 18	Week 52	Month 24	Month 36	Month 48	Month 60
Placebo	2736	2630	2534	2326	1523	1509	791	477
Ertugliflozin	5479	5305	5081	4723	3162	3179	1746	1053

†Full analysis set included all randomised participants who received one or more doses of blinded study medication and had one or more measurements of the analysis endpoint.
CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least squares mean; SEM, standard error of the mean.

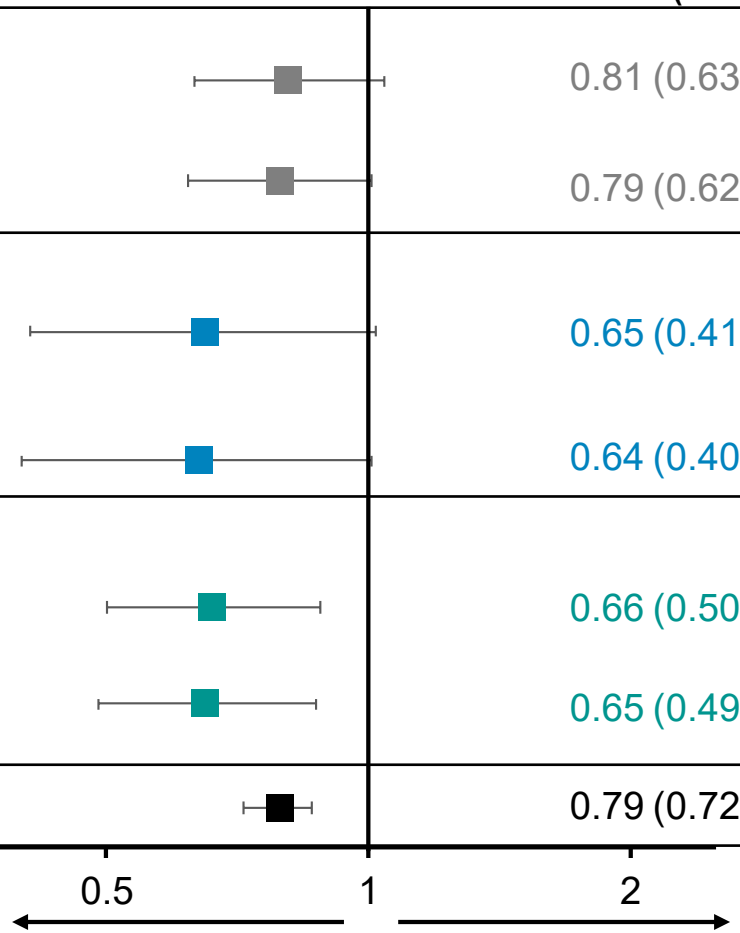
VERTIS CV: Mean eGFR over time by UACR category†



†Full analysis set included all randomised participants who received one or more doses of blinded study medication and had one or more measurements of the analysis endpoint.
CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least squares mean; UACR, urinary albumin-to-creatinine ratio.

VERTIS CV: Forest plot of the key kidney outcomes†

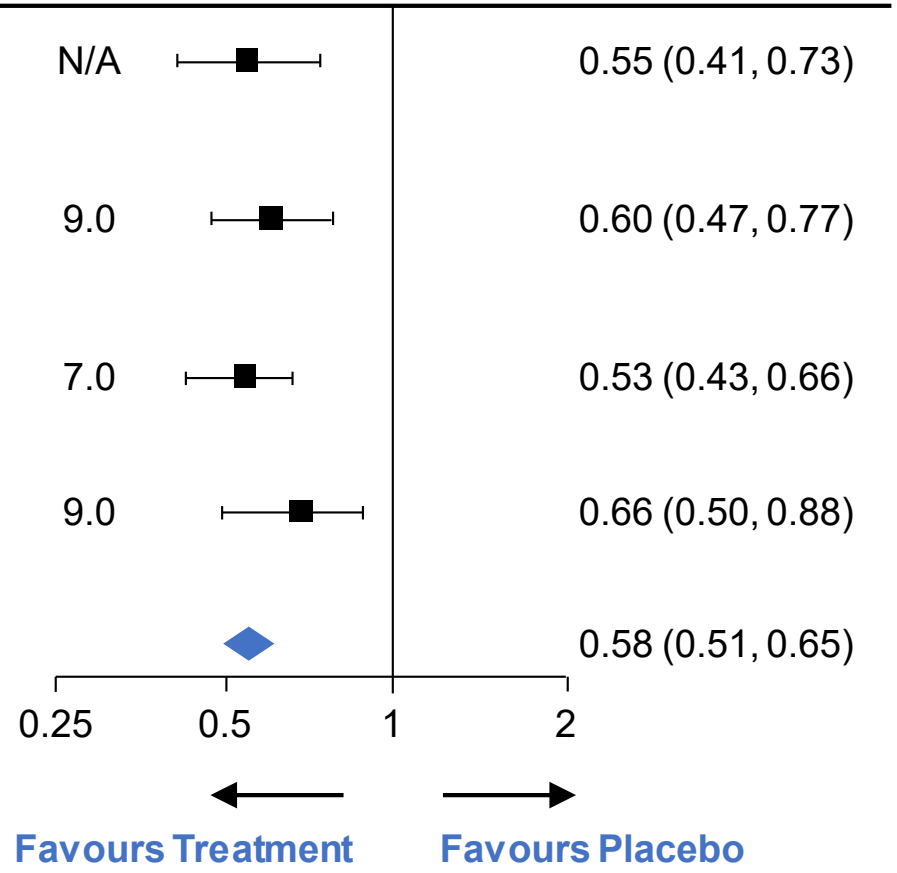
Endpoint	Placebo N=2747 Event rate per 1000 person-years	Ertugliflozin N=5499 Event rate per 1000 person-years	HR (95% CI)	*P* value
Composite of doubling of serum creatinine, kidney dialysis/transplant or renal death	11.5	9.3	0.81 (0.63, 1.04)	0.08
Doubling of serum creatinine	11.2	8.9	0.79 (0.62, 1.01)	0.06
Sensitivity analysis for the risk of the composite of sustained doubling of baseline serum creatinine, chronic kidney dialysis/transplant or renal death	3.5	2.3	0.65 (0.41, 1.02)	0.06
Sustained doubling of serum creatinine	3.4	2.1	0.64 (0.40, 1.01)	0.06
Composite of sustained 40% reduction in eGFR, chronic kidney dialysis/transplant or renal death	9.0	6.0	0.66 (0.50, 0.88)	<0.01
Sustained 40% reduction in eGFR	8.8	5.8	0.65 (0.49, 0.87)	<0.01
Progression of albuminuria	120.7	94.8	0.79 (0.72, 0.86)	<0.01



†Intention-to-treat analysis set that included all randomised patients.
CI, confidence interval; HR, hazard ratio; NA, not applicable.

Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

	Treatment		Placebo		Hazard Ratio (95% CI)
	Events/N (%)	Rate per 1000 Patient-years	Events/N (%)	Rate per 1000 Patient-years	
EMPA-REG OUTCOME[1]	100/4645 (2.15)	N/A	86/2323 (3.70)	N/A	0.55 (0.41, 0.73)
CANVAS Programme[2]	124/5795 (2.14)	5.5	125/4347 (2.88)	9.0	0.60 (0.47, 0.77)
DECLARE-TIMI 58[3]	127/8582 (1.48)	3.7	238/8578 (2.77)	7.0	0.53 (0.43, 0.66)
VERTIS CV	113/5499 (2.05)	6.0	85/2747 (3.09)	9.0	0.66 (0.50, 0.88)
Pooled estimate (Q statistic *P*=0.64; I^2=0.0%)					0.58 (0.51, 0.65)



Intention-to-treat analysis set.
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio.
[1]Perkovic V et al. *Nephrol Dial Transplant.* 2019:1–9; [2]Neal B et al. *N Engl J Med.* 2017;377:644–657; [3]Wiviott SD et al. *N Engl J Med.* 2019;380:347–357.

Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

	Kidney composite outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.55** (0.41, 0.73)
CANVAS Programme[2]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.60** (0.47, 0.77)
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2 and/or end-stage renal disease and/or renal death	**0.53** (0.43, 0.66)
VERTIS CV*	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.66** (0.50, 0.88)

*Pre-specified exploratory, intention-to-treat analysis set, 95.0% CI.
CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio. [1]Post-hoc exploratory, Perkovic V et al. *Nephrol Dial Transplant* (2019) 1–9; [2]Pre-specified exploratory, Neal B et al. *N Engl J Med* 2017;377:644-657; [3]Pre-specified secondary, Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

Summary and conclusion

- The results of VERTIS CV provide further evidence supporting the beneficial effects of this drug class on CV and kidney outcomes:
  - Ertugliflozin reduced the risk of the pre-specified exploratory renal composite, which included a sustained 40% decline in eGFR, chronic renal replacement therapy or renal death
    - The relative risk reduction for the kidney composite was similar across CKD stage, level of UACR and KDIGO CKD risk category, demonstrating consistent kidney benefits regardless of how CKD was defined
  - Significantly reduced UACR in patients with a range of albuminuria at baseline; preserved kidney function, especially in patients with macroalbuminuria at greatest risk of DKD progression
  - eGFR declined acutely with ertugliflozin and was then better preserved over time compared with placebo

CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease; SGLT2, sodium-glucose cotransporter 2; UACR, urinary albumin-to-creatinine ratio.

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