Finerenone in patients with CKD and T2D by SGLT-2i treatment: an analysis of the FIDELIO-DKD study

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RATIONALE AND OBJECTIVE

- In FIDELIO-DKD, finerenone reduced the incidence of cardiorenal events in patients with CKD and T2D, without an effect on blood glucose[1]
- The objective of this analysis was to explore the treatment effect of finerenone in patients with concomitant SGLT-2i use, either at baseline or during the trial

KEY FINDINGS

- The benefits of finerenone on kidney and CV outcomes in patients with CKD and T2D appeared consistent in the absence or presence of SGLT-2i use at baseline (interaction *p*-value 0.21 and 0.46, respectively), or at any time during the trial
- This analysis also demonstrated a reduction in UACR with finerenone compared with placebo, even in patients using SGLT-2i at baseline. The magnitude of reduction in UACR is consistent for patients with and without SGLT2i use at baseline

CKD, chronic kidney disease; CV, cardiovascular; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229

DISCLOSURES
Professor Rossing has received the following:

Consultancy and/or speaking fees (paid to his institution) from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, Eli Lilly, Merck, MSD, Mundipharma, Novo Nordisk, and Sanofi Aventis

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GF reports lectures fees and/or that he is a committee member of trials and registries sponsored by Bayer, Novartis, Vifor, Medtronic, Servier, Amgen, and Boehringer Ingelheim. He is a Senior Consulting Editor for *JACC Heart Failure,* and he has received research support from the European Union. **RA** reports personal fees and non-financial support from Bayer Healthcare Pharmaceuticals Inc., during the conduct of the study; he also reports personal fees and non-financial support from Akebia Therapeutics, Janssen, Relypsa, Vifor Pharma, Boehringer Ingelheim, Sanofi, Eli Lilly, AstraZeneca, and Fresenius; he has received personal fees from Ironwood Pharmaceuticals, Merck & Co., Lexicon, and Reata; and non-financial support from Otsuka America Pharmaceutical, OPKO Pharmaceuticals, and E. R. Squibb & Sons; he is a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene; a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa; a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen; he has served as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate; and he has received research grants from the U.S. Veterans Administration and the National Institutes of Health. **SDA** has received research support from Abbott Vascular and Vifor International, and personal fees from Abbott Vascular, Boehringer Ingelheim, Bayer, BRAHMS, Novartis, Servier, Vifor International, Impulse Dynamics, and Cardiac Dimensions. **BP** reports consultant fees for Bayer, AstraZeneca, Sanofi/Lexicon, scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sarfez, PhaseBio, Vifor/Relypsa, Cereno Scientific, Ardelyx, KBP Biosciences, Boehringer Ingelheim, Brainstorm Medical, and Tricida; he has stock options for Ardelyx, KBP Biosciences, SQ Innovation, Sarfez, scPharmaceuticals, Cereno Scientific, G3 Pharmaceuticals, Vifor/Relypsa, Brainstorm Medical, and Tricida; he also holds a patent for site-specific delivery of eplerenone to the myocardium (US patent #9931412), and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (provisional patent US 63/045,784). **LMR** has no disclosures. **JC** has received research grants and/or consultancy fees and speaker honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Pfizer, Sanofi, and Servier. **AK** reports research funding, paid to the Bethesda Diabetes Research Center Netherlands, from AstraZeneca, Novo Nordisk, MSD, and Sanofi Aventis. **KM** is a grant holder with AstraZeneca and reports consultancy fees and speaker honoraria for AstraZeneca, Bayer, Napp, Oncacare, Pharmacosmos, and Vifor Fresenius. **GS** has received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Mundipharma, and Takeda. **CW** has received honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli-Lilly, and MSD. **AJ** and **MFS** are full-time employees of Bayer AG, Germany; MFS is also a shareholder in Bayer, Novo Nordisk, and Eli Lilly. **CS** is a full-time employee of Bayer PLC, United Kingdom. **GLB** reports research funding, paid to the University of Chicago Medicine, from Bayer, during the conduct of the study; he also reports research funding, paid to the University of Chicago Medicine, from Novo Nordisk and Vascular Dynamics; he acted as a consultant and received personal fees from for Merck, Relypsa, and Alnylam; he is an Editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, and Section Editor of UpToDate; and he is an Associate Editor of *Diabetes Care* and *Hypertension Research*.

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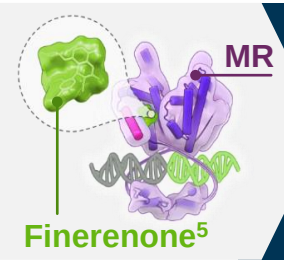
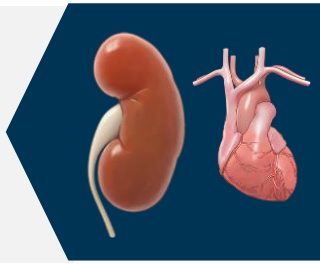
Despite SGLT-2i treatment being recommended for patients with CKD and diabetes,[1] further treatment options are needed



Finerenone is a **novel, nonsteroidal, selective MRA** that **inhibits MR overactivation** leading to **inflammation and fibrosis** in preclinical models, and was investigated in the phase III FIDELIO-DKD trial in patients with **CKD and T2D**[2–4]

Findings from FIDELIO-DKD, which included patients receiving optimized RAS therapy, demonstrated that finerenone lowers the risk of CKD progression and CV events in patients with CKD and T2D[2]



Results from CREDENCE and DAPA-CKD have shown that SGLT-2is offer kidney protection and lower the risk of CV events; however, in these studies, CKD progression or kidney failure still occurred in ~10% of patients and CV events in ~8% of patients after a median follow-up of ~2.5 years*[6,7]

*Based on the mean of primary composite kidney outcomes (decline in eGFR of ≥50%, end-stage kidney disease, or death from renal or CV causes), and CV outcomes (cardiovascular death, myocardial infarction, stroke or hospitalisation for heart failure) in both studies

eGFR, estimated glomerular filtration rate; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int 2020;98:S1–S115; 2. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229; 3. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 4. Filippatos G, *et al. Circulation* 2021;143:540–552; 5. Agarwal R, *et al. Eur Heart J* 2021;42:152–161; 6. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306; 7. Heerspink HJL, *et al. N Engl J Med* 2020;383:1436–1446

FIDELIO-DKD included adults with CKD and T2D with/without SGLT-2i use at baseline[1,2]

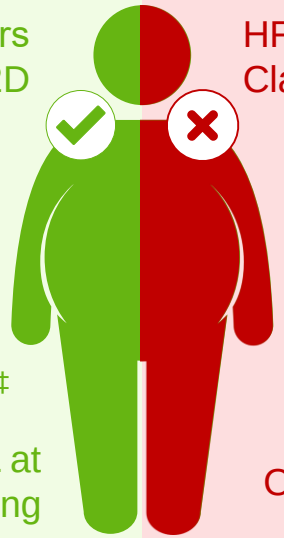
5734 patients randomized — **2.6 years' median follow-up**

Run-in (4–16 weeks) → Screening → **R 1:1**

- **Finerenone 10 or 20 mg od***
- **Placebo**

Key inclusion criteria

- Aged ≥18 years with T2D
- On max. tolerated dose of ACEi or ARB for ≥4 weeks
- eGFR ≥25 to <75 mL/min/1.73 m^2#
- UACR ≥30 to ≤5000 mg/g‡
- Serum [K$^+$] ≤4.8 mmol/L at run-in and screening



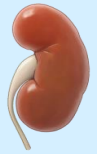
Key exclusion criteria

- HFrEF with NYHA Class II–IV
- Uncontrolled arterial hypertension §
- HbA1c >12%
- Other kidney disease¶

Key endpoints

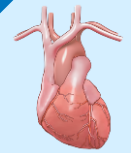
1. Kidney composite

Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death**



2. CV composite

Time to CV death, non-fatal MI, non-fatal stroke, or HHF##



Aim of this subgroup analysis

To explore the treatment effect of finerenone in patients with and without concomitant SGLT-2i use

SGLT-2i use was permitted at any time during the trial but was not mandated

*10 mg if screening eGFR <60 mL/min/1.73 m^2; 20 mg if ≥60 mL/min/1.73 m^2, up-titration encouraged from month 1 if serum potassium ≤4.8 mmol/L and eGFR stable; a decrease in the dose from 20 to 10 mg od was allowed any time after the initiation of finerenone or placebo; #patients either had an eGFR of ≥25 to <60 and with UACR ≥30 to <300 mg/g and diabetic retinopathy, or eGFR ≥25 to <75 with UACR ≥300 mg/g; ‡patients with moderately elevated albuminuria (UACR 30–300 mg/g) were required to also have an eGFR ≥25 to <60 mL/min/1.73 m^2 and diabetic retinopathy; §mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit; ¶known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis; **primary composite kidney outcome defined as end-stage kidney disease (initiation of dialysis for ≥90 days or kidney transplantation) or eGFR <15 mL/min/1.73 m^2, a sustained decrease of ≥40% in eGFR from baseline maintained for ≥4 weeks, and death from renal causes;[1] ##secondary composite CV outcome included the number of patients with CV death, non-fatal MI, non-fatal stroke or HHF[1]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; [K$^+$], potassium concentration; MI, myocardial infarction; NYHA, New York Heart Association; od, once daily; R, randomization; SBP, systolic blood pressure

1. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344

Patients treated with SGLT-2i at baseline had higher eGFR and HbA1c, and lower median UACR and SBP than those without

Patient characteristic*	No SGLT-2i (n=5415)	SGLT-2i (n=259)
Age, years	66±9	63±10
Race, White	3412 (63)	180 (70)
Black/AA	255 (5)	9 (4)
Asian	1382 (26)	58 (22)
Sex, male	3795 (70)	188 (73)
SBP, mmHg	138±14[#]	135±14
BMI, kg/m^2	31±6[‡]	32±6
Duration of diabetes, years	17±9[§]	17±9
HbA1c, %	7.7±1.5[§]	8.0±1.2
eGFR, mL/min/1.73 m^2	44±13[¶]	51±12
Serum potassium, mmol/L	4.4±0.5[¶]	4.3±0.4
UACR, mg/g, median (IQR)	866 (456–1653)**	619 (370–1258)
History of CV disease	2488 (46)	117 (45)

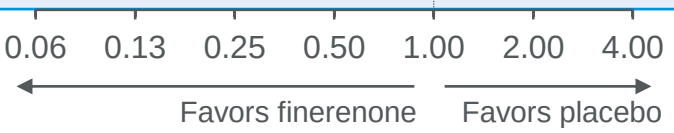
Medication use, n (%)	No SGLT-2i (n=5415)	SGLT-2i (n=259)
ACEi	1865 (34)	77 (30)
ARB	3543 (65)	182 (70)
Diuretics	3069 (57)	145 (56)
Statins	3992 (74)	223 (86)
Potassium-lowering agents	131 (2)	5 (2)
Glucose-lowering therapies	5265 (97)	259 (100)
Insulin and analogs	3464 (64)	173 (67)
GLP-1RA	346 (6)	48 (19)

At baseline, 259 (4.6%) patients were receiving SGLT-2i. After the study start, SGLT-2i was initiated as a new medication in 328 (5.8%) patients.

*Values are n (%) or mean ± SD unless otherwise stated. Symbols indicate data missing for the stated number of patients: [#]n=5; [‡]n=17; [§]n=11; [¶]n=2; **n=3
AA, African American; BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; SD, standard deviation

Kidney benefit was consistent irrespective of SGLT-2i use at baseline and during the trial

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)*	*p*-interaction*
Primary composite kidney outcome#				
Overall FIDELIO-DKD population[1]	504/2833 (17.8)	600/2841 (21.1)	0.82 (0.73–0.93)	
No SGLT-2i at baseline	490/2709 (18.1)	590/2706 (21.8)	0.82 (0.72–0.92)	0.21
SGLT-2i at baseline	14/124 (11.3)	10/135 (7.4)	1.38 (0.61–3.10)	
Secondary composite kidney outcome‡				
Overall FIDELIO-DKD population[1]	252/2833 (8.9)	326/2841 (11.5)	0.76 (0.65–0.90)	
No SGLT-2i at baseline	249/2709 (9.2)	320/2706 (11.8)	0.77 (0.65–0.91)	0.54
SGLT-2i at baseline	3/124 (2.4)	6/135 (4.4)	0.50 (0.12–1.99)	



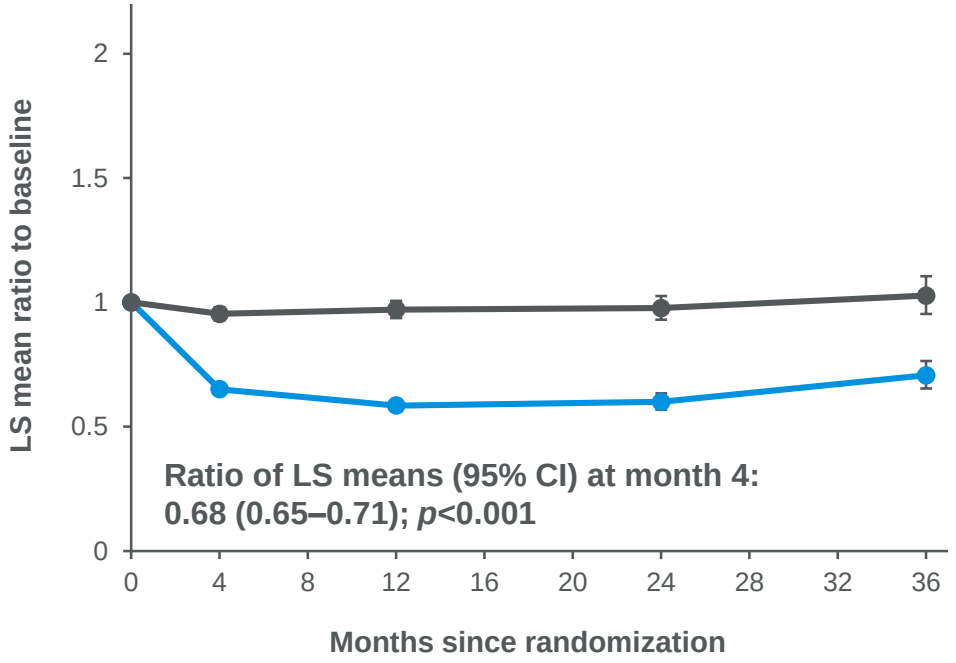
Finerenone benefit for the primary kidney outcome was also consistent regardless of SGLT-2i use at any time (*p*-value for interaction 0.83)§

*Hazard ratios (95% CI) and interaction *p*-values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup, and a subgroup by treatment interaction term as fixed effects; #primary composite kidney outcome defined as end-stage kidney disease (initiation of dialysis for ≥90 days or kidney transplantation) or eGFR <15 mL/min/1.73 m^2, a sustained decrease of ≥40% in eGFR from baseline maintained for ≥4 weeks, and death from renal causes[1]; ‡secondary composite kidney outcome of kidney failure, a sustained decrease of at least 57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for ≥4 weeks, or death from renal causes[1]; § Cox proportional hazards model after forward selection (including the following variables: age at run-in, BMI at baseline, baseline C-reactive protein, baseline hemoglobin in blood, baseline serum creatinine, baseline serum albumin, baseline systolic blood pressure, and duration of diabetes at baseline) was also used to determine the effect of SGLT-2i use at any time during the trial, including SGLT-2i use as a time-dependent covariate. CI, confidence interval

1. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229

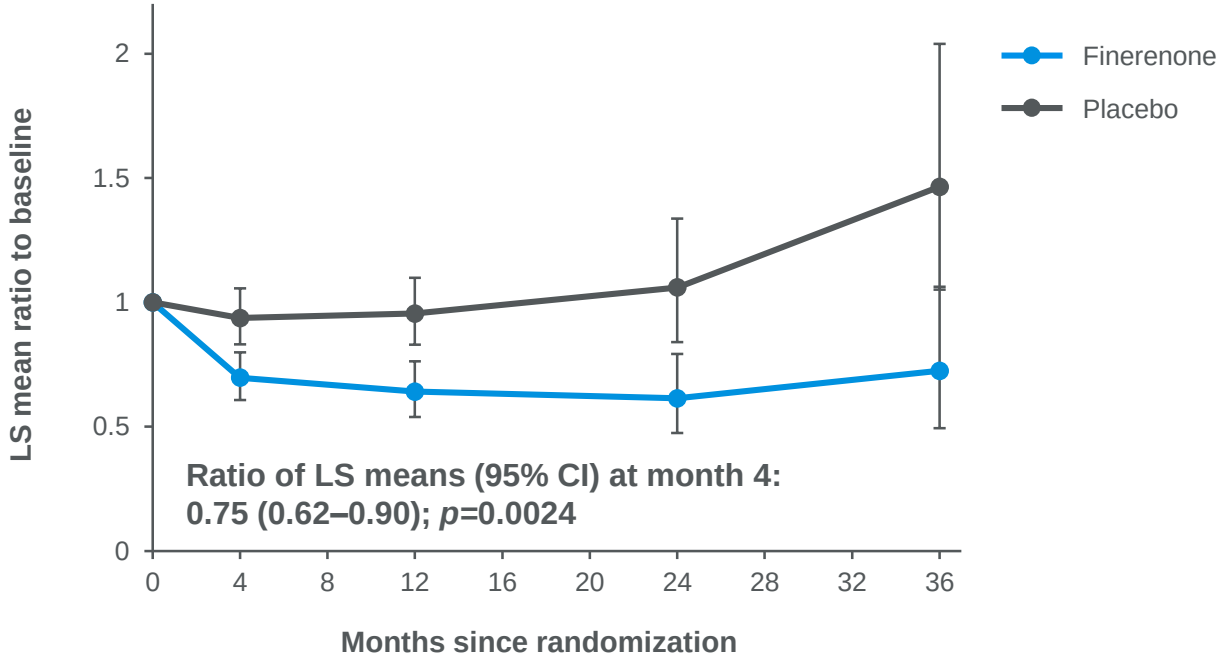
The change in UACR from baseline to month 4 was consistent irrespective of SGLT-2i use at baseline

Without SGLT-2i



No. of patients				
Finerenone	2604	2465	1769	818
Placebo	2597	2471	1742	798

With SGLT-2i



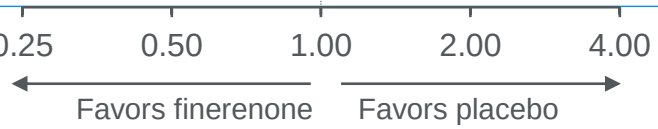
No. of patients				
Finerenone	121	117	72	38
Placebo	129	127	83	36

Full analysis set. Mixed model with factors for treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates

LS, least squares

CV benefit was consistent irrespective of SGLT-2i use at baseline and during the trial

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)*	*p*-interaction*
Key secondary composite CV# outcome				
Overall FIDELIO-DKD population[1]	367/2833 (13.0)	420/2841 (14.8)	0.86 (0.75–0.99)	
No SGLT-2i at baseline	352/2709 (13.0)	405/2706 (15.0)	0.85 (0.74–0.98)	0.46
SGLT-2i at baseline	15/124 (12.1)	15/135 (11.1)	1.12 (0.55–2.30)	



Finerenone benefit for the key secondary CV outcome was also consistent regardless of SGLT-2i use at any time (*p*-value for interaction 0.26)‡

*Hazard ratios (95% CI) and interaction *p*-values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup, and a subgroup by treatment interaction term as fixed effects; #secondary composite CV outcome included the number of patients with CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure[1]; ‡Cox proportional hazards model after forward selection (including the following variables: history of CV disease, diuretics use at baseline, age at run-in, baseline HbA1c, baseline C-reactive protein, baseline serum creatinine, baseline serum albumin, and baseline systolic blood pressure) was also used to determine the effect of SGLT-2i use at any time during the trial, including SGLT-2i use as a time-dependent covariate.

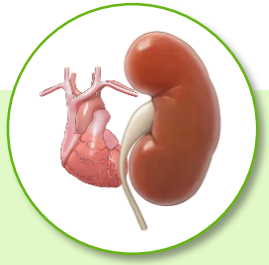
1. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229

Overall safety outcomes were consistent, with treatment-emergent hyperkalemia-related events lower in patients with SGLT-2i use at baseline compared to those without

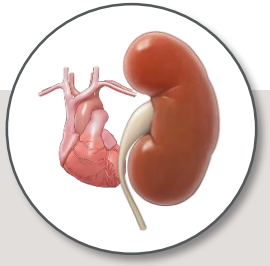
Treatment-emergent AE, n (%)	No SGLT-2i at baseline		SGLT-2i at baseline	
	Finerenone (n=2703)	Placebo (n=2696)	Finerenone (n=124)	Placebo (n=135)
Any AE	2355 (87.1)	2361 (87.6)	113 (91.1)	117 (86.7)
Related to study drug	621 (23.0)	434 (16.1)	25 (20.2)	15 (11.1)
Leading to permanent discontinuation	202 (7.5)	161 (6.0)	5 (4.0)	7 (5.2)
Any SAE	863 (31.9)	931 (34.5)	39 (31.5)	40 (29.6)
Related to study drug	47 (1.7)	34 (1.3)	1 (0.8)	0
Leading to permanent discontinuation	71 (2.6)	77 (2.9)	4 (3.2)	1 (0.7)
AE with outcome death	30 (1.1)	49 (1.8)	1 (0.8)	2 (1.5)
Treatment-emergent hyperkalemia AE, n (%)				
Any AE	506 (18.7)	251 (9.3)	10 (8.1)	4 (3.0)
Related to study drug	328 (12.1)	132 (4.9)	5 (4.0)	3 (2.2)
Leading to permanent discontinuation	63 (2.3)	24 (0.9)	1 (0.8)	1 (0.7)
Treatment-emergent AEs of interest by system organ class (>5% patients)				
Hypertension	205 (7.6)	262 (9.7)	7 (5.6)	11 (8.1)
Hypoglycemia	147 (5.4)	187 (6.9)	4 (3.2)	7 (5.2)

AE, adverse event; GLP-1RA, glucagon-like peptide-1 receptor agonist; SAE, serious adverse event; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

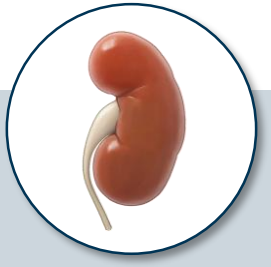
Conclusions



Consistent kidney and CV benefits of finerenone vs placebo, irrespective of SGLT-2i use at baseline or at any time during the trial



Patients treated with SGLT-2is at baseline had higher mean eGFR, lower median UACR, and lower SBP



Reduction in UACR with finerenone observed in both groups

Results were independent of SGLT-2i use at baseline; a consistent magnitude of UACR reduction was demonstrated in patients with and without SGLT-2i use at baseline

Overall safety was similar, with a lower number of hyperkalemia events in those treated with SGLT-2i at baseline