Efficacy and safety of finerenone in patients with CKD and T2D by GLP-1RA treatment

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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]
- This analysis aimed to report outcomes in FIDELIO-DKD by GLP-1RA use at baseline and during the trial

KEY FINDINGS

- Finerenone reduced the relative risk of the primary kidney composite outcome by 18% and the key secondary CV composite outcome by 14%[1]
  - Results were consistent regardless of GLP-1RA use at baseline (*p*-interaction 0.15 and 0.51, respectively)
  - Cardiorenal benefit was also consistent considering GLP-1RA use during the trial
- Reduction in UACR with finerenone was observed in patients with or without GLP-1RA use at baseline and during the trial
  - Results were independent of GLP-1RA use, with a potential benefit for UACR reduction on top of baseline GLP-1RA use

CKD, chronic kidney disease; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; 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 Pharma Inc, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Merck, MSD, Mundipharma, Novo Nordisk, Sanofi, and Vifor Pharma

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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, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fresenius, Janssen, Relypsa, Sanofi, and Vifor Pharma; he has received personal fees from Ironwood Pharmaceuticals, Lexicon, Merck & Co., and Reata, and non-financial support from E. R. Squibb & Sons, Opko Pharmaceuticals, and Otsuka America Pharmaceutical; 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, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor International. **GF** reports lectures fees and that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, and Vifor. He is a Senior Consulting Editor for *JACC Heart Failure,* and he has received research support from the European Union. **BP** has received consultant fees from Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Phasebio, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; he has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; 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. **AA** has served on advisory boards or consulted for Aspen Pharmacare, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck SA, Novo Nordisk and Servier. **MM** is a consultant for the Novo Nordisk Algerian subsidiary and has received personal fees from Bayer AG, Merck, Novo Nordisk, Servier, and Sharp and Dohme during the past 3 years. **AJ** is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. **AL** is a full-time employee of Bayer SA, Division Pharmaceuticals, Brazil. **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 Alnylam, Merck, and Relypsa; 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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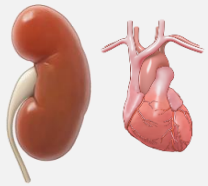
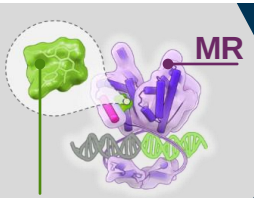
GLP-1RA treatment is recommended for some patients with T2D and CKD[1]



CKD is a **leading cause of morbidity and mortality** in patients with **T2D**,[2–4] with the presence of CKD increasing the risk of CV disease, hypertension, and death[2–5]

Several agents already approved for use in patients with T2D have demonstrated **CV and renal benefits**, including **GLP-1RAs**[1]



Finerenone is a **novel**, **nonsteroidal, selective MRA** that **inhibits inflammation** and **fibrosis**, and it has been shown to reduce the risk of **CV disease** and **CKD progression** in patients with **CKD** and **T2D**[6,7]

This analysis examines outcomes in FIDELIO-DKD by GLP-1RA use at baseline and during the trial, because patients with CKD and T2D may be treated with GLP-1RAs in clinical practice

FIDELIO-DKD

MRA, mineralocorticoid receptor agonist

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2020;98:S1–S115; 2. Gorriz JL, *et al. J Clin Med* 2020;9:947; 3. Greco EV, *et al. Medicina (Kaunas)* 2019;55:233; 4. Kawanami D, Takashi Y. *Front Pharmacol* 2020;11:967; 5. Yin WL, *et al. Diabetes Ther* 2020;11:835–844; 6. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229; 7. Filippatos G, *et al. Circulation* 2021;143:540–552; 8. Agarwal R, *et al. Eur Heart J* 2021;42:152–161

FIDELIO-DKD included adults with CKD and T2D with or without GLP-1RA use at baseline[1,2]

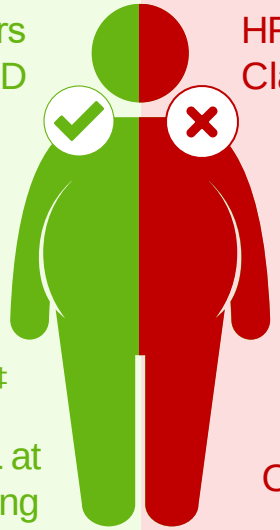
5734 patients randomized — **2.6 years' median follow-up**

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



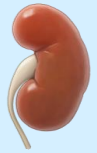
Key exclusion criteria

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

Key endpoints

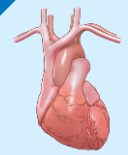
1. Kidney composite

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



2. CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF##



Aim of this subgroup analysis

To evaluate the impact of baseline GLP-1RA treatment on composite kidney and CV outcomes and safety in patients treated with finerenone or placebo

*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 once daily 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 to 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;[2] ##secondary composite CV outcome included the number of patients with CV death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure[2]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; 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 GLP-1RAs at baseline had higher HbA1c, lower median UACR, and a longer duration of diabetes versus those without

Patient characteristics*	No GLP-1RA (n=5280)	GLP-1RA (n=394)
Age, years	66±9	64±8
Race, White	3304 (63)	288 (73)
Black/African American	238 (5)	26 (7)
Asian	1375 (26)	65 (17)
Sex, male	3713 (70)	270 (69)
SBP, mmHg	138±14	139±14
BMI, kg/m^2	31±6	34±6
Duration of diabetes, years	16±9	18±8
HbA1c, %	7.7±1.4	7.9±1.2
eGFR, mL/min/1.73 m^2	44±13	45±12
Serum potassium, mmol/L	4.4±0.5	4.3±0.4
UACR, mg/g, median (IQR)	860 (452–1635)	749 (409–1576)
History of CV disease	2439 (46)	166 (42)

Medication use, n (%)	No GLP-1RA (n=5280)	GLP-1RA (n=394)
ACEi	1819 (35)	123 (31)
ARB	3455 (65)	270 (69)
Diuretics	2962 (56)	252 (64)
Statins	3888 (74)	327 (83)
Potassium lowering agents	129 (2)	7 (2)
Glucose-lowering therapies	5130 (97)	394 (100)
Insulin and analogues	3354 (64)	283 (72)
SGLT-2 inhibitors	211 (4)	48 (12)
GLP-1RAs	5280 (100)	394 (100)
DPP-4 inhibitors	1502 (28)	20 (5)
Sulfonylureas	1250 (24)	48 (12)
Metformin	2277 (43)	213 (54)
α-glucosidase inhibitors	308 (6)	16 (4)

At baseline, 394 (6.9%) of patients were receiving a GLP1-RA.

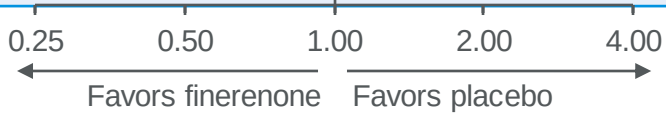
GLP-1RA was initiated as a new medication in 368 (6.5%) patients

*Values are n (%) or mean ± SD unless otherwise stated

BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; IQR, interquartile range; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2

Kidney benefit was consistent irrespective of GLP-1RA use at baseline and during the trial[1]

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 GLP-1RA at baseline	472/2644 (17.9)	568/2636 (21.5)	0.80 (0.71–0.91)	0.15
GLP-1RA at baseline	32/189 (16.9)	32/205 (15.6)	1.17 (0.71–1.90)	
Secondary composite kidney outcome‡				
Overall FIDELIO-DKD population[1]	252/2833 (8.9)	326/2841 (11.5)	0.76 (0.65–0.90)	
No GLP-1RA at baseline	234/2644 (8.9)	306/2636 (11.6)	0.75 (0.63–0.88)	0.33
GLP-1RA at baseline	18/189 (9.5)	20/205 (9.8)	1.04 (0.55–1.96)	



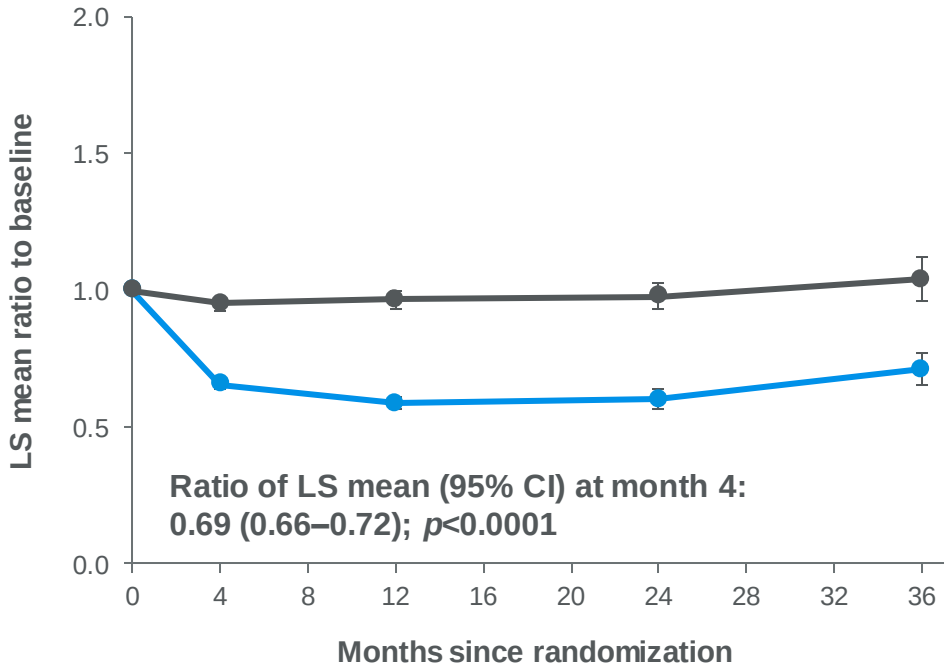
The benefit of finerenone on the primary kidney outcome was also consistent regardless of GLP-1RA use at any time (*p*-value for interaction 0.31)¶; however, the small sample size of patients taking a GLP-1RA makes it difficult to interpret the results

#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]; *hazard ratios (95% CI) are based on the stratified Cox proportional hazards model estimated within each level of the subgroup variable; §interaction *p*-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including the terms treatment group, baseline subgroup, and their interaction. ¶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 GLP-1RA use at any time during the trial, including GLP-1RA 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 GLP-1RA use at baseline

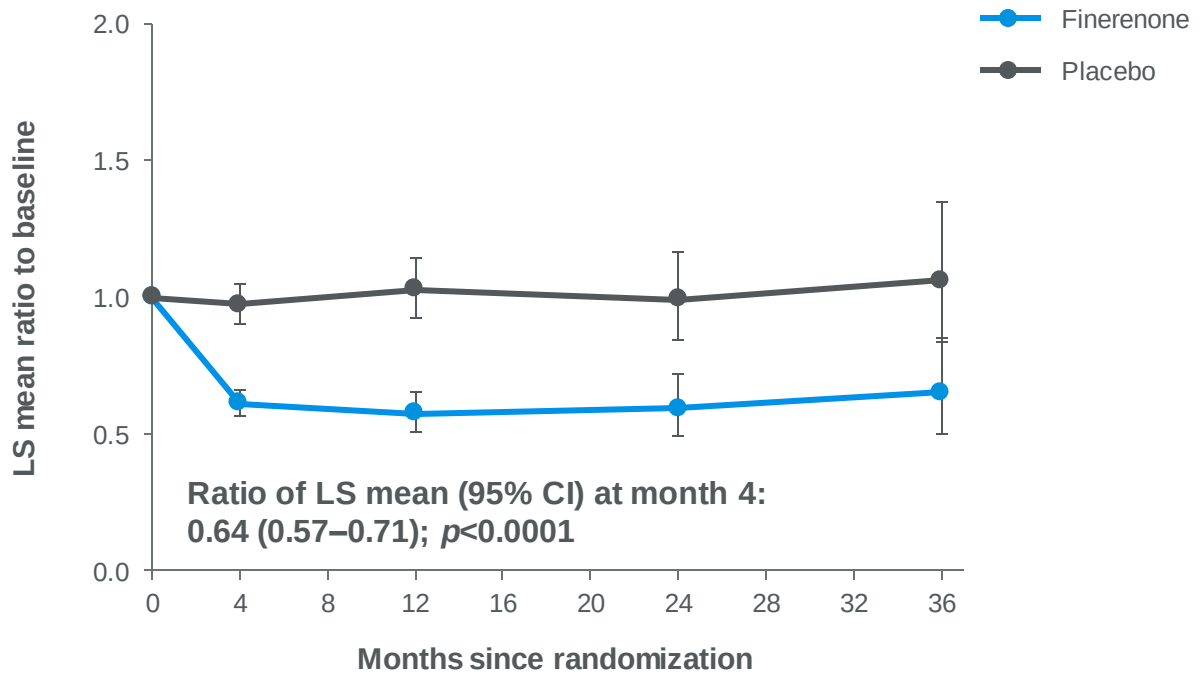
No GLP-1RA



No. of patients

Finerenone	2539	2415	1728	789
Placebo	2529	2408	1695	761

GLP-1RA



No. of patients

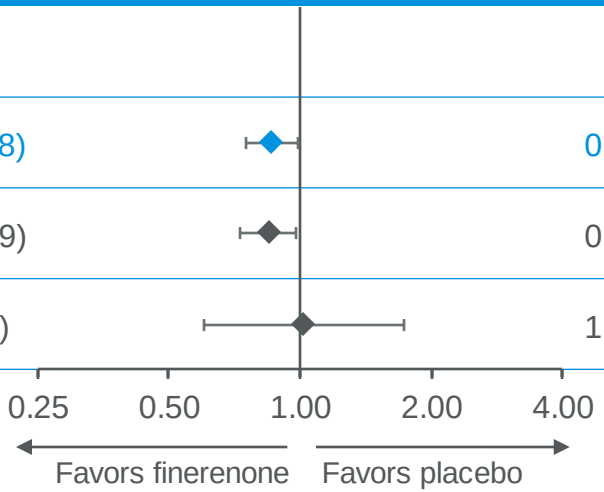
Finerenone	186	167	113	67
Placebo	197	190	130	73

Full analysis set. Mixed model with factors 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 covariate

LS, least-squares

CV benefit was consistent irrespective of GLP-1RA use at baseline and during the trial[1]

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)[#]	*p*-interaction[‡]
Secondary composite CV outcome*				
Overall FIDELIO-DKD population[1]	367/2833 (13.0)	420/2841 (14.8)	0.86 (0.75–0.99)	
No GLP-1RA at baseline	340/2644 (12.9)	392/2636 (14.9)	0.85 (0.73–0.98)	0.51
GLP-1RA at baseline	27/189 (14.3)	28/205 (13.7)	1.02 (0.60–1.74)	



Finerenone benefit for the key secondary CV outcome was also consistent regardless of GLP-1RA use at any time (*p*-value for interaction 0.86)[§]

*Secondary composite CV outcome included the number of patients with CV death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure; [#]hazard ratios (95% CI) are based on the stratified Cox proportional hazards model estimated within each level of the subgroup variable[1]; [‡]interaction *p*-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including the terms treatment group, baseline subgroup, and their interaction; [§] Cox proportional hazards model after forward selection (including the following variables: history of CVD, diuretics use at baseline, age at run-in, BMI at baseline, 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 GLP-1RA use at any time during the trial, including GLP-1RA use as a time-dependent covariate

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

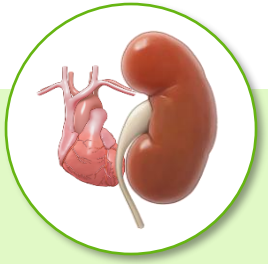
Overall safety and incidence of investigator-reported hyperkalemia were similar between patients who received GLP-1RAs at baseline compared with those who did not (safety analysis set)

Treatment-emergent AE, n (%)	No GLP-1RA at baseline		GLP-1RA at baseline	
	Finerenone (n=2638)	Placebo (n=2628)	Finerenone (n=189)	Placebo (n=203)
Any AE	2292 (86.9)	2288 (87.1)	176 (93.1)	190 (93.6)
Related to study drug	594 (22.5)	414 (15.8)	52 (27.5)	35 (17.2)
Leading to permanent discontinuation	188 (7.1)	152 (5.8)	19 (10.1)	16 (7.9)
Any SAE	835 (31.7)	902 (34.3)	67 (35.4)	69 (34.0)
Related to study drug	44 (1.7)	32 (1.2)	4 (2.1)	2 (1.0)
Leading to permanent discontinuation	70 (2.7)	74 (2.8)	5 (2.6)	4 (2.0)
AE with outcome death	31 (1.2)	50 (1.9)	0 (0.0)	1 (0.5)
Treatment-emergent hyperkalemia AE, n (%)				
Any AE	480 (18.2)	235 (8.9)	36 (19.0)	20 (9.9)
Related to study drug	309 (11.7)	126 (4.8)	24 (12.7)	9 (4.4)
Leading to permanent discontinuation	58 (2.2)	22 (0.8)	6 (3.2)	3 (1.5)

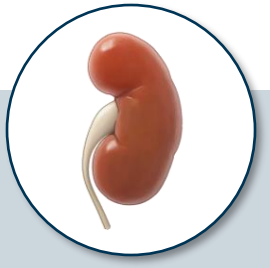
Of the patients who received a GLP-1RA at baseline, treatment-emergent AEs of interest (in >5% patients), included: acute kidney injury (6.9% versus 9.5%) and hypoglycemia (5.9% versus 4.8%) in placebo and finerenone groups, respectively*

*Other treatment-emergent AEs of interest included: hypovolemia: no GLP-1RA, finerenone 4 (0.2%), placebo 1 (<0.1%); GLP-1RA, finerenone 0, placebo 0; pancreatitis: no GLP-1RA, finerenone 1 (<0.1%), placebo 3 (0.1%); GLP-1RA, finerenone 1 (0.5), placebo 0; acute pancreatitis: no GLP-1RA, finerenone 7 (0.3%), placebo 9 (0.1%); GLP-1RA, finerenone 0, placebo 0; chronic pancreatitis: no GLP-1RA, finerenone 5 (0.2%), placebo 6 (0.2%); GLP-1RA, finerenone 0, placebo 0; medullary thyroid carcinoma: none in any treatment groups. AE, adverse event; SAE, serious adverse event

Conclusions



Consistent kidney and CV benefits of finerenone versus placebo, irrespective of GLP-1RA use[1]



Reduction in UACR with finerenone observed in both groups

Results were independent of GLP-1RA use at baseline, with a potential benefit for UACR reduction on top of baseline GLP-1RA use

Overall safety and hyperkalemia incidence were similar in patients with and without GLP-1RA use

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