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Incidence and predictors of hyperkalemia in patients with CKD and T2D in the FIDELIO-DKD trial

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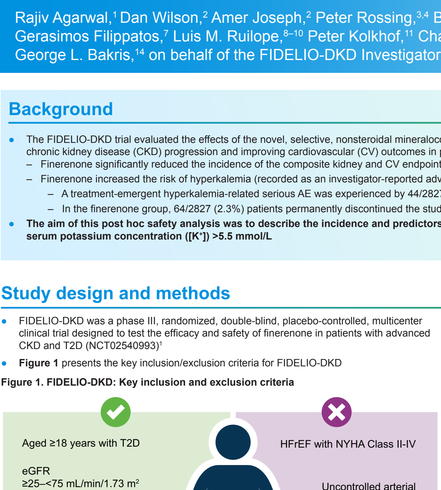
Background

- The FIDELIO-DKD trial evaluated the effects of the novel, selective, nonsteroidal mineralocorticoid receptor antagonist finerenone, in addition to standard of care, on slowing chronic kidney disease (CKD) progression and improving cardiovascular (CV) outcomes in patients with advanced CKD and type 2 diabetes (T2D)[1]
  - Finerenone significantly reduced the incidence of the composite kidney and CV endpoints by 18% and 14%, respectively
  - Finerenone increased the risk of hyperkalemia (recorded as an investigator-reported adverse event [AE]) compared with placebo
    - A treatment-emergent hyperkalemia-related serious AE was experienced by 44/2827 (1.6%) patients in the finerenone group and 12/2831 (0.4%) patients in the placebo group
    - In the finerenone group, 64/2827 (2.3%) patients permanently discontinued the study drug due to hyperkalemia, compared with 25/2831 (0.9%) patients in the placebo group
- **The aim of this post hoc safety analysis was to describe the incidence and predictors of hyperkalemia in FIDELIO-DKD, assessed by central laboratory evaluation of serum potassium concentration ([K$^+$]) >5.5 mmol/L**

Study design and methods

- FIDELIO-DKD was a phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial designed to test the efficacy and safety of finerenone in patients with advanced CKD and T2D (NCT02540993)[1]
- **Figure 1** presents the key inclusion/exclusion criteria for FIDELIO-DKD

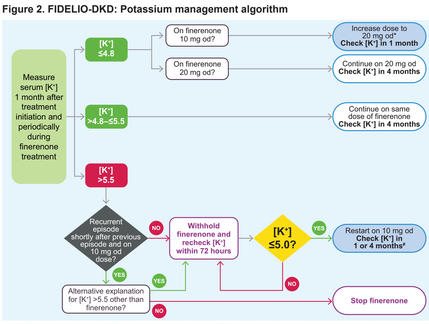
Figure 1. FIDELIO-DKD: Key inclusion and exclusion criteria



*Patients with moderately elevated albuminuria were required to also have 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.
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; [K$^+$], potassium concentration; NYHA, New York Heart Association; SBP, systolic blood pressure; T2D, type 2 diabetes.

- CKD was defined as a urine albumin-to-creatinine ratio (UACR) ≥30–<5000 mg/g and an estimated glomerular filtration rate (eGFR) ≥25–<75 mL/min/1.73 m^2
- Initial dosing of finerenone (10 mg or 20 mg once daily [od]) was based on eGFR at screening (25–<60 or ≥60 mL/min/1.73 m^2, respectively)
- Patients had serum [K$^+$] <4.8 mmol/L recorded at two separate visits (run-in and screening)
  - At baseline (randomization) patients were still permitted to be randomized even if serum [K$^+$] was ≥4.8 mmol/L
- During the study, serum [K$^+$] levels were monitored at every study visit, by local and central laboratories – local laboratory serum [K$^+$] values (and eGFR changes) were used to guide study drug dosing
  - Serum [K$^+$] was measured at Month 1, Month 4, and every 4 months thereafter
  - Finerenone was temporarily withheld if serum [K$^+$] was >5.5 mmol/L, and it was restarted at 10 mg od when serum [K$^+$] was ≤5.0 mmol/L (**Figure 2**)

Figure 2. FIDELIO-DKD: Potassium management algorithm



*If eGFR was stable; stable eGFR was defined as a decrease ≤30% since last available measurement; # 1 month if treatment interruption was >7 days, 4 months if treatment interruption was ≤7 days
eGFR, estimated glomerular filtration rate; [K$^+$], potassium concentration; od, once daily.

Post-hoc safety analysis

- Hyperkalemia was defined as one of the following:
  - An investigator-reported AE using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased' (subjective assessment)
  - Serum [K$^+$] >5.5 mmol/L according to quantitative assessment measured by a central laboratory
- Events were considered treatment-emergent if they occurred after the start of finerenone administration and up to 3 days after any interruption of study drug

Statistical analyses

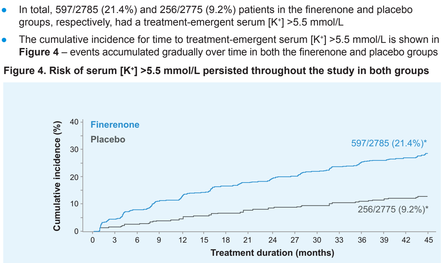
- Multivariate Cox proportional hazards regression was used to examine associations between baseline characteristics and any post-baseline serum [K$^+$] >5.5 mmol/L, adjusting for treatment assignment and baseline covariates chosen *a priori* based on clinical factors known to affect serum [K$^+$]. A *p*-value <0.05 was used to determine a significant association
- The analysis was performed on the safety analysis set (all randomized patients without critical Good Clinical Practice violations who took ≥1 dose of study drug), using SAS software, version 9.4 (SAS Institute, Cary, NC)

Results

Changes in serum [K$^+$]

- At baseline (randomization), 769/5658 (13.6%) patients had serum [K$^+$] >4.8 mmol/L (**Figure 3**)

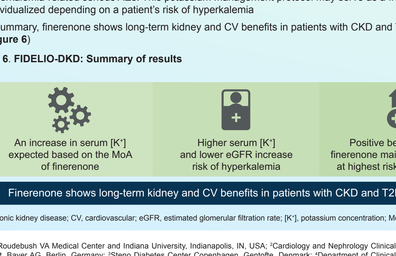
Figure 3. Serum [K$^+$] at baseline (randomization)



[K$^+$], potassium concentration.

- **Table 1** presents baseline characteristics of patients with vs without any serum [K$^+$] >5.5 mmol/L during the study
- In total, 597/2785 (21.4%) and 256/2775 (9.2%) patients in the finerenone and placebo groups, respectively, had a treatment-emergent serum [K$^+$] >5.5 mmol/L
- The cumulative incidence for time to treatment-emergent serum [K$^+$] >5.5 mmol/L is shown in **Figure 4** – events accumulated gradually over time in both the finerenone and placebo groups

Figure 4. Risk of serum [K$^+$] >5.5 mmol/L persisted throughout the study in both groups



Patients at risk**	2785	2603	2425	2253	2147	2056	1898	1650	1356	1178	970	777	580	445	318	183
	2775	2672	2571	2453	2349	2251	2128	1881	1524	1310	1076	865	648	499	375	221
Patients with events	0	125	216	303	357	381	440	471	502	512	541	561	578	583	588	594
	0	44	73	104	135	148	175	199	216	220	230	241	246	250	254	256

Cumulative incidence calculated by Aalen-Johansen estimator using all-cause death as a competing risk.
*n/N (%) over 2.6 years median follow-up; **patients at risk must have both a baseline and post-baseline treatment-emergent value and the baseline value must be below the threshold.

Multivariate analysis of risk factors for serum [K$^+$] >5.5 mmol/L

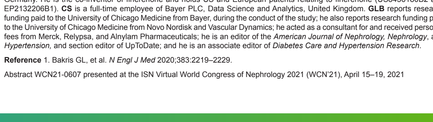
- Baseline risk factors for hyperkalemia that were significantly associated with an increased risk of serum [K$^+$] >5.5 mmol/L, independent of other variables, were female sex, increasing serum [K$^+$], lower eGFR, higher UACR, beta-blocker use, and assignment to finerenone versus placebo (hazard ratio [HR]=2.13; 95% confidence interval [CI] 1.86–2.45) (**Figure 5**)
  - Baseline diuretic use (HR=0.76; 95% CI 0.66–0.87) or sodium-glucose co-transporter-2 inhibitor (SGLT-2i) use (HR=0.45; 95% CI 0.27–0.75) and advanced age were significantly associated with a lower risk of hyperkalemia
- After a median follow-up of 2.6 years, FIDELIO-DKD demonstrated a positive benefit–risk ratio with finerenone that was maintained in patients at highest risk of hyperkalemia (data not shown)

Table 1. Baseline characteristics and medications

	No serum [K$^+$] >5.5 mmol/L (n=4604)	Any[a] serum [K$^+$] >5.5 mmol/L (n=1054)
Sex, male	3279 (71.2)	694 (65.8)
Age, years	65.8±9.0	64.5±9.1
Serum [K$^+$], mmol/L	4.3±0.4	4.7±0.5
eGFR, mL/min/1.73 m^2	44.8±12.4	42.2±12.9
Median UACR (IQR), mg/g	820 (440–1565)	957 (479–1918)
Label-recommended dose of optimized RASi		
≤ minimum	1368 (29.7)	331 (31.4)
> minimum to < maximum	1125 (24.4)	263 (25.0)
≥ maximum	2096 (45.5)	458 (43.5)
Missing	15 (0.3)	2 (0.2)
Beta-blocker	2405 (52.2)	560 (53.1)
Potassium lowering agents (including binders)	91 (2.5)	45 (4.3)
Diuretic	2677 (58.1)	527 (50.0)
SGLT-2i	222 (6.2)	19 (1.8)
Assigned to the finerenone group	2151 (46.7)	676 (64.1)

Data are n (%) or mean ± standard deviation unless stated otherwise.
[a]Includes both non-treatment-emergent and treatment-emergent events.
eGFR, estimated glomerular filtration rate; [K$^+$], potassium concentration; IQR, interquartile range; RASi, renin–angiotensin system inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

Figure 5. Multivariate regression analysis of time to any post-baseline serum [K+] >5.5 mmol/L (Cox proportional hazards model, safety analysis set)



*UACR was modeled as a continuous variable. One unit change in Log2 UACR denotes doubling of UACR; #according to dose recommended in the product label, optimized at the maximum dose that did not cause unacceptable side effects.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; [K$^+$], potassium concentration; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

Discussion

- This analysis identified several baseline factors independently associated with the risk of hyperkalemia in patients with moderate to advanced CKD and T2D
  - These included age, sex, serum [K$^+$], eGFR, UACR, diuretic use, beta-blocker use, and SGLT-2i use
  - Baseline optimization of ACE inhibitor or ARB treatment did not increase the risk of hyperkalemia
- Finerenone treatment increased the risk of hyperkalemia independent of other risk factors (HR=2.13; 95% CI 1.86–2.45)
- The potassium management protocol implemented in FIDELIO-DKD minimized the clinical impact of hyperkalemia, as demonstrated by the low frequency of clinically meaningful hyperkalemia-related serious AEs. This potassium management protocol may serve as a framework for potassium monitoring in clinical practice, with the frequency of monitoring individualized depending on a patient's risk of hyperkalemia
- In summary, finerenone shows long-term kidney and CV benefits in patients with CKD and T2D. Elevations in serum [K$^+$] are predictable and manageable through routine monitoring (**Figure 6**)

Figure 6. FIDELIO-DKD: Summary of results

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; [K$^+$], potassium concentration; MoA, mechanism of action; T2D, type 2 diabetes.

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

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