

**Hyperkalemia Risk with Finerenone: Results from the
FIDELIO-DKD Trial**

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22 **Abstract:** Background: Finerenone reduced risk of cardiorenal outcomes in patients with CKD
23 and type 2 diabetes in the FIDELIO-DKD trial. We report incidences and risk factors for hyperkalemia
24 with finerenone and placebo in FIDELIO-DKD.
25

26 Methods: This <i>post hoc</i> safety analysis defined hyperkalemia as â€™mild or
27 â€™moderate based on serum potassium concentrations of >5.5 or >6.0 mmol/L, respectively, assessed
28 at all regular visits. Cumulative incidences of hyperkalemia were based on the Aalenâ€™™Johansen
29 estimator using death as competing risk. A multivariate Cox proportional hazards model identified
30 significant independent predictors of hyperkalemia. Restricted cubic splines assessed relationships
31 between short-term post-baseline changes in serum potassium or eGFR and subsequent hyperkalemia
32 risk. During the study, serum potassium levels guided drug dosing. Patients in either group who
33 experienced â€™mild hyperkalemia had the study drug withheld until serum potassium was â€™5.0
34 mmol/L; then the drug was restarted at the 10 mg daily dose. Placebo-treated patients underwent sham
35 treatment interruption and downtitration.
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39 Results: Over 2.6 yearsâ€™™ median follow-up, 597/2785 (21.4%) and 256/2775 (9.2%) of
40 patients treated with finerenone and placebo, respectively, experienced treatment-emergent â€™mild
41 hyperkalemia; 126/2802 (4.5%) and 38/2796 (1.4%) patients, respectively, experienced moderate
42 hyperkalemia. Independent risk factors for â€™mild hyperkalemia were higher serum potassium, lower
43 eGFR, increased urine albumin-to-creatinine ratio, younger age, female sex, beta-blocker use, and
44 finerenone assignment. Diuretic or sodium-glucose co-transporter-2 inhibitor use reduced risk. In both
45 groups, short-term increases in serum potassium and decreases in eGFR were associated with
46 subsequent hyperkalemia. At month 4, the magnitude of increased hyperkalemia risk for any change
47 from baseline was smaller with finerenone than with placebo
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50 Conclusions: Finerenone was independently associated with hyperkalemia. However, routine
51 potassium monitoring and hyperkalemia management strategies employed in FIDELIO-DKD minimized
52 the impact of hyperkalemia, providing a basis for clinical use of finerenone.
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Significance Statement

Hyperkalemia is common following treatment with a mineralocorticoid receptor antagonist (MRA). In the FIDELIO-DKD randomized trial, the nonsteroidal MRA finerenone improved cardiorenal outcomes, but was associated with a 2-fold higher risk of hyperkalemia versus placebo, consistent across patient subgroups. Short-term increases in serum potassium and decreases in eGFR with finerenone or placebo were associated with subsequent hyperkalemia; at month 4, the magnitude of the increased hyperkalemia risk for any given change from baseline was smaller with finerenone than with placebo. Routine potassium monitoring, with temporary treatment interruption and dose reduction in the event of hyperkalemia, is necessary for the safe use of finerenone to protect the kidneys and cardiovascular system of patients with CKD and T2D.

Hyperkalemia Risk with Finerenone: Results from the FIDELIO-DKD Trial

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* The full member list of the FIDELIO-DKD Investigators is extensive and can be found in the supplement.

Abstract

Background: Finerenone reduced risk of cardiorenal outcomes in patients with CKD and type 2 diabetes in the FIDELIO-DKD trial. We report incidences and risk factors for hyperkalemia with finerenone and placebo in FIDELIO-DKD.

Methods: This *post hoc* safety analysis defined hyperkalemia as \geq mild or \geq moderate based on serum potassium concentrations of >5.5 or >6.0 mmol/L, respectively, assessed at all regular visits. Cumulative incidences of hyperkalemia were based on the Aalen–Johansen estimator using death as competing risk. A multivariate Cox proportional hazards model identified significant independent predictors of hyperkalemia. Restricted cubic splines assessed relationships between short-term post-baseline changes in serum potassium or eGFR and subsequent hyperkalemia risk. During the study, serum potassium levels guided drug dosing. Patients in either group who experienced \geq mild hyperkalemia had the study drug withheld until serum potassium was ≤ 5.0 mmol/L; then the drug was restarted at the 10 mg daily dose. Placebo-treated patients underwent sham treatment interruption and downtitration.

Results: Over 2.6 years' median follow-up, 597/2785 (21.4%) and 256/2775 (9.2%) of patients treated with finerenone and placebo, respectively, experienced treatment-emergent \geq mild hyperkalemia; 126/2802 (4.5%) and 38/2796 (1.4%) patients, respectively, experienced moderate hyperkalemia. Independent risk factors for \geq mild hyperkalemia were higher serum potassium, lower eGFR, increased urine albumin-to-creatinine ratio, younger age, female sex, beta-blocker use, and finerenone assignment. Diuretic or sodium-glucose co-transporter-2 inhibitor use reduced risk. In both groups, short-term increases in serum potassium and decreases in eGFR were associated with subsequent hyperkalemia. At month 4, the magnitude of increased hyperkalemia risk for any change from baseline was smaller with finerenone than with placebo.

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5 **Conclusions:** Finerenone was independently associated with hyperkalemia. However,
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7 routine potassium monitoring and hyperkalemia management strategies employed in
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9 FIDELIO-DKD minimized the impact of hyperkalemia, providing a basis for clinical use of
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11 finerenone.
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Introduction

Drugs that interrupt the renin–angiotensin system (RAS) are the backbone of therapy in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D).¹⁻³ Above the kidney protection offered by a single RAS inhibitor, dual-agent RAS inhibition was evaluated for kidney protection in patients with CKD and T2D in several randomized controlled trials.⁴⁻⁶ No kidney or cardiovascular (CV) benefits were apparent but an increased risk of adverse events (AEs), including acute kidney injury and hyperkalemia, was seen.⁴⁻⁶

The Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease (FIDELIO-DKD) trial evaluated the effects of the novel, selective, nonsteroidal mineralocorticoid receptor (MR) antagonist (MRA) finerenone, in addition to standard of care, including a maximum tolerated dose of a single RAS inhibitor, to slow CKD progression and reduce the risk of CV outcomes in patients with CKD and T2D. Finerenone significantly reduced the relative risk versus placebo of the primary composite kidney-specific outcome by 18% (absolute risk reduction of 3.3%) and the key secondary composite CV outcome by 14% (absolute risk reduction of 1.8%).⁷ Consistent with the known role of the MR in the regulation of electrolyte and fluid homeostasis,⁸ MR antagonism with finerenone increased the incidence of any hyperkalemia (an investigator-reported AE) compared with placebo in a patient population at high intrinsic risk of hyperkalemia.⁷

Here, we report the incidence and risk factors associated with hyperkalemia defined quantitatively by central laboratory assessment of serum potassium concentration ($[K^+]$) measured at every study visit (using thresholds of >5.5 mmol/L for \geq mild hyperkalemia and >6.0 mmol/L for \geq moderate hyperkalemia, in accordance with latest KDIGO guidance on severity of acute hyperkalemia⁹). We describe the cumulative incidence of hyperkalemia, the associated risk factors, the interaction of finerenone with these risk factors, and measures taken to mitigate the risk of hyperkalemia during the study. Lastly, we contextualize the risk

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3 of hyperkalemia with finerenone compared with the risk associated with the use of dual RAS
4 inhibition and steroidal MR antagonism.
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8 **Methods**

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11 The FIDELIO-DKD trial (NCT02540993) design and details have been published previously.⁷
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13 Briefly, FIDELIO-DKD was a phase 3, randomized, double-blind, placebo-controlled,
14
15 multicenter clinical trial testing the efficacy and safety of finerenone in patients with advanced
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17 CKD and T2D. The trial was performed in accordance with the principles of the Declaration
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19 of Helsinki and was approved by International Review Boards, independent Ethics
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21 Committees, and competent authorities according to national and international regulations.
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27 **Patients and Study Design**

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29 Patients were included in the trial if they were treated with a maximum tolerated labelled
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31 dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker
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33 (ARB), but not both, with a serum $[K^+]$ ≤ 4.8 mmol/L at both the run-in and screening visits.
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35 CKD was defined as either: (1) persistent, moderately elevated albuminuria (urine albumin-
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37 to-creatinine ratio [UACR] ≥ 30 – <300 mg/g), an estimated glomerular filtration rate (eGFR)
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39 ≥ 25 – <60 mL/min/1.73 m², and a history of diabetic retinopathy; or (2) persistent severely
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41 elevated albuminuria (UACR ≥ 300 – ≤ 5000 mg/g) and an eGFR ≥ 25 – <75 mL/min/1.73 m².
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43 Exclusion criteria included treatment with a steroidal MRA, renin inhibitor, or potassium-
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45 sparing diuretic that could not be discontinued ≥ 4 weeks prior to the screening visit.
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51 Eligible patients were randomized 1:1 to receive oral finerenone or placebo using a
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53 computer-generated randomizations schedule and stratified by region (North America,
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55 Europe, Asia, Latin America, other), albuminuria at screening (moderately increased,
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57 severely increased), and eGFR at screening (25 – <45 , 45 – <60 , ≥ 60 mL/min/1.73 m²). All
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3 patients, investigators, and study personnel (except for the independent data monitoring
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5 committee) were masked to treatment allocation.
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9 The study consisted of run-in, screening, and double-blind treatment periods. During the
10 run-in period (4–16 weeks), RAS inhibitor therapy was uptitrated to the maximum tolerated
11 labelled dose, maintained for ≥ 4 weeks prior to the screening visit. Patients meeting eligibility
12 criteria at the screening visit were subsequently randomized within 2 weeks. Patients
13 received an initial dose of study drug of 10 or 20 mg once daily (od), based on an eGFR at
14 the screening visit of $25 < \text{eGFR} < 60$ or ≥ 60 mL/min/1.73 m², respectively. After the start of
15 treatment, study drug dose reduction or temporary treatment interruption was allowed at any
16 time for safety reasons.
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29 **Serum [K⁺] Assessment and Management of Hyperkalemia**

31 At regular study visits (month 1, month 4, and every 4 months thereafter), study drug dosing
32 was based on serum [K⁺] and eGFR, assessed at local laboratories (Figure 1). If serum [K⁺]
33 was ≤ 4.8 mmol/L, the dose of study drug was either uptitrated from 10 mg to 20 mg od
34 (provided any eGFR decrease was $< 30\%$ from the last measured value) or maintained at the
35 20 mg od dose. If serum [K⁺] was > 4.8 – ≤ 5.5 mmol/L, treatment was continued with the same
36 dose of study drug. When serum [K⁺] was > 5.5 mmol/L, study drug was temporarily withheld
37 and serum [K⁺] rechecked within 72 hours – at this point, if serum [K⁺] was ≤ 5.0 mmol/L,
38 study drug was restarted at the 10 mg od dose; otherwise study drug continued to be
39 withheld until serum [K⁺] was ≤ 5.0 mmol/L. Because this was a double-blind trial, placebo
40 recipients underwent sham up- and downtitration depending on their serum [K⁺], and had
41 temporary placebo interruption if serum [K⁺] was > 5.5 mmol/L, in the same manner as for the
42 finerenone group.
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3 The protocol specified that serum [K⁺] should be measured within 4 weeks (±7 days) after a
4 temporary treatment interruption of ≥7 days or after dose adjustments or uptitration of study
5 drug. If the treatment interruption was <7 days, serum [K⁺] was measured within 4 months, at
6 the next scheduled study visit. Permanent discontinuation of study drug was recommended if
7 a patient on the 10 mg od dose experienced a recurrent hyperkalemia event soon after a
8 previous event with interruption of study drug (provided the only explanation for the recurring
9 hyperkalemia event was the study drug), or if, in the opinion of the investigator, continuation
10 of treatment was harmful to the patient (Figure 1).
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22 Except for temporary treatment interruption and subsequent dose reductions of study drug in
23 response to elevations in serum [K⁺], management of hyperkalemia was at the investigator's
24 discretion based on local guidance. There were no restrictions on the use of potassium
25 supplements or potassium binders during the trial, and a low-potassium diet was not
26 mandated by the protocol. Irrespective of serum [K⁺], investigators were instructed to
27 maintain standard-of-care therapy; dose reduction of concomitant RAS inhibitor therapy was
28 not allowed solely to facilitate the maintenance of study drug.
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40 **Outcomes**

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42 The primary outcome of this *post hoc* safety analysis was ≥mild or ≥moderate hyperkalemia,
43 defined using serum [K⁺] thresholds of >5.5 and >6.0 mmol/L, respectively, as assessed
44 quantitatively by the central laboratory at every study visit. Hyperkalemia was also reported
45 as an investigator-reported AE using the Medical Dictionary for Regulatory Activities
46 (MedDRA) preferred terms 'hyperkalemia' and 'blood potassium increased', as reported
47 previously.⁷ AEs, including elevations in serum [K⁺], were considered as treatment emergent
48 if they started or worsened during study drug intake or up to 3 days after any temporary or
49 permanent interruption.
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3 As reported previously, the primary efficacy outcome of the FIDELIO-DKD study was a
4 composite of time to first onset of kidney failure, a sustained $\geq 40\%$ decrease in eGFR from
5 baseline over ≥ 4 weeks, or renal death. The key secondary efficacy outcome was a
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7 composite of time to first onset of CV death, nonfatal myocardial infarction, nonfatal stroke,
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9 or hospitalization for heart failure.^{7,10}
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13 14 15 **Statistical Analyses**

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17 Safety analyses were performed in the safety analysis set (all randomized patients without
18 critical Good Clinical Practice [GCP] violations who took ≥ 1 dose of study drug). Cumulative
19 incidences of hyperkalemia were based on the Aalen–Johansen estimator using death as a
20 competing risk; for the serum $[K^+]$ analyses, patients with elevated baseline values (>5.5 and
21 >6.0 mmol/L, respectively) were censored at day 1. The following baseline variables were
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23 used in a multivariate Cox proportional hazards model (model 1) to identify significant
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25 independent predictors of \geq mild or \geq moderate hyperkalemia. The variables were selected
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27 following a review of the literature and were those deemed biologically plausible by the study
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29 investigators. They included the following: age, sex, eGFR categories, serum $[K^+]$ categories,
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31 log₂ transformed UACR, RAS inhibitor dosing, diuretic use, beta-blocker use, sodium-
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33 glucose co-transporter-2 inhibitor (SGLT-2i) use, and study drug assignment. A significance
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35 threshold of $P < 0.05$ was used to identify significant, independent predictors. Schoenfeld
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37 residuals were used to check if the proportional hazards assumption was satisfied for each
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39 baseline variable used in the model. Another multivariate Cox proportional hazards model
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41 (model 2) was used to describe the interaction of the study drug with each of the baseline
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43 variables included in model 1 described above. Model 2 evaluated whether the treatment
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45 effect of finerenone on risk of \geq mild or \geq moderate hyperkalemia differed within the
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47 subgroups; the likelihood ratio test of the nested models was reported as the P -value of the
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49 interaction. Restricted cubic splines were used to capture any possible nonlinear effects of
50
51 the short-term change in serum $[K^+]$ or eGFR (from baseline to month 1 or 4) and the
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53 subsequent risk of hyperkalemia. The likelihood ratio test was used for the nested models
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3 with and without using the spline function to assess whether the model using splines was a
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5 better fit to the data than the standard linear model. The hazard ratio and 95% confidence
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7 intervals were plotted for the variable where the spline function had been applied. These
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9 values compared a change in the relevant variable with that of a zero change within each
10
11 treatment group.
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15 Efficacy analyses were performed in the full analysis set, which included all randomized
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17 patients excepting 60 patients with critical GCP violations. In time-to-event analyses, the
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19 superiority of finerenone versus placebo was tested via a stratified log-rank test; stratification
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21 factors were region, eGFR category at screening, and albuminuria category at screening; the
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23 statistical assumptions of FIDELIO-DKD have been published previously.⁷ All analyses were
24
25 performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).
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31 **Data Sharing**

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33 Data from this study will be made available in the public domain – the electronic repository
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35 and date of data availability will be confirmed by Bayer AG.
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41 **Role of the funding source**

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43 The FIDELIO-DKD trial was sponsored by Bayer AG. The Executive Committee designed
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45 and oversaw conduct of the trial, in collaboration with the sponsor. Analyses were conducted
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47 by the sponsor, and all authors had access to and participated in the interpretation of the
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49 data and made the decision to submit for publication.
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Results

Serum [K⁺] at Run-in, Screening, and Baseline

Between September 2015 and June 2018, 13,911 patients were enrolled, of whom 8177 did not meet eligibility criteria at the run-in or screening visits; 5734 patients were subsequently randomized. At the run-in visit, potassium values were available for 12,010/13,911 patients, of whom 2181 (18.2%) had a serum [K⁺] >4.8 mmol/L and were excluded. At the screening visit, 640/7114 (9.0%) patients had a serum [K⁺] >4.8 mmol/L and were screen-failed. At baseline, the mean serum [K⁺] was 4.37±0.46 mmol/L in the finerenone group and 4.38±0.46 mmol/L in the placebo group. The proportion of patients with a baseline serum [K⁺] ≤4.8 mmol/L versus >4.8 mmol/L was 4889/5658 (86.4%) and 769/5658 (13.6%), respectively. A total of 390 (6.9%) patients had a baseline serum [K⁺] >5.0 mmol/L (Figure S1).

Changes in Serum [K⁺] During the Study

Patients treated with finerenone had higher mean serum [K⁺] compared with placebo recipients. The maximum difference between treatment groups was 0.23 mmol/L at month 4 and was consistent across predefined screening eGFR categories (Figure S2). Over 2.6 years of median follow-up, 597/2785 (21.4%) and 256/2775 (9.2%) patients in the finerenone and placebo groups, respectively, experienced treatment-emergent ≥mild hyperkalemia. A total of 126/2802 (4.5%) patients in the finerenone group and 38/2796 (1.4%) patients in the placebo group had treatment-emergent ≥moderate hyperkalemia. At month 1, 86/2742 (3.1%) and 14/2757 (0.5%) patients in the finerenone group and 34/2730 (1.2%) and 4/2749 (0.1%) patients in the placebo group had serum [K⁺] >5.5 and >6.0 mmol/L, respectively; hyperkalemia events accumulated gradually throughout the study in both treatment groups (Figure 2).

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3 Compared with patients without \geq mild hyperkalemia, patients with treatment-emergent \geq mild
4 hyperkalemia tended to have lower eGFR, higher albuminuria, and higher serum $[K^+]$ at
5 baseline, and were more likely to be treated with a potassium binder but less likely to be
6 treated with a diuretic or an SGLT-2i (Tables 1 and S1). Similar differences were observed
7 between patients with and without treatment-emergent \geq moderate hyperkalemia (Tables S2
8 and S3).
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19 **Multivariate Analysis of Risk Factors for \geq mild and \geq moderate Hyperkalemia**

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21 A multivariate Cox proportional hazards regression model identified baseline risk predictors
22 for \geq mild (Figure 3) and \geq moderate (Figure S3) hyperkalemia. Higher baseline serum $[K^+]$
23 was associated with an increased risk of \geq mild hyperkalemia; the risk was increased 1.5-,
24 2.8-, and 4.2-fold in patients with serum $[K^+]$ of 4.5–<4.8, 4.8–5.0, and >5.0 mmol/L at
25 baseline, respectively, compared with a serum $[K^+]$ of 4.1–4.5 mmol/L. Likewise, lower eGFR
26 was an independent predictor of hyperkalemia; compared with an eGFR \geq 60 mL/min/1.73
27 m^2 , the risk of \geq mild hyperkalemia increased 1.5-fold and 2-fold as eGFR dropped below 45
28 and 25 mL/min/1.73 m^2 , respectively. Patients with an eGFR of 45–<60 mL/min/1.73 m^2 had
29 a similar risk to those with an eGFR \geq 60 mL/min/1.73 m^2 . Every doubling of UACR was
30 associated with a 1.1-fold increased risk of hyperkalemia. Finally, compared with placebo,
31 assignment to finerenone doubled the risk of hyperkalemia, after adjustment for all other risk
32 factors included in the model. Baseline diuretic or SGLT-2i use and advanced age were
33 associated with lower risk of \geq mild hyperkalemia; baseline RAS inhibitor dosing did not
34 modify hyperkalemia risk.
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53 The magnitude of the increased risk of \geq mild and \geq moderate hyperkalemia with finerenone
54 versus placebo was consistent across subgroups, including sex, baseline CKD severity, and
55 baseline medication use (Figures S4 and S5). Significant treatment interactions were noted
56 for the risk of \geq mild hyperkalemia by baseline serum $[K^+]$ and age (Figure S4).
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Short-term Changes in Serum [K⁺] and eGFR and the Future Risk of Hyperkalemia

Irrespective of treatment assignment, the risk of \geq mild hyperkalemia was higher in patients with larger increases in serum [K⁺] between baseline and month 1 (Figure 4A) or month 4 (Figure 4B) compared with those with no change in serum [K⁺] ($P<0.001$ for both time points). At month 1, for any given increase in serum [K⁺], the magnitude of the increased risk of \geq mild hyperkalemia was similar between treatment groups, compared with no change in each respective group ($P=0.233$; Figure 4A). However, at month 4, the relationship between changes in serum [K⁺] and subsequent risk of \geq mild hyperkalemia was significantly different between groups ($P=0.011$; Figure 4B); a placebo recipient with a 0.5 mmol/L increase in serum [K⁺] had an approximately 3.4-fold higher risk of hyperkalemia than a patient with no change in serum [K⁺], whereas with finerenone, a 0.5 mmol/L increase in serum [K⁺] was associated with a 2-fold higher risk of hyperkalemia compared with no change. A similar pattern was observed for changes in eGFR at month 1 (Figure 4C) and month 4 (Figure 4D) and the subsequent risk of \geq mild hyperkalemia. At month 1, patients with a greater decrease in eGFR from baseline were at higher risk of subsequent hyperkalemia ($P<0.001$) than patients with no change in eGFR, and the magnitude of the increased risk for any given decrease in eGFR was similar between treatment groups ($P=0.134$; Figure 4C). A greater decrease in eGFR from baseline to month 4 compared with no change in eGFR was also associated with an increased risk of developing hyperkalemia during the study ($P<0.001$); however, the relationship was significantly different between treatment groups ($P=0.034$; Figure 4D). A placebo-treated patient with a 5 mL/min/1.73 m³ decrease in eGFR had a 1.4-fold higher risk of hyperkalemia than a patient with no change in eGFR, whereas a finerenone recipient with a 5 mL/min/1.73 m³ decrease in eGFR had the same risk of hyperkalemia as one with no change in eGFR.

Management of Hyperkalemia During the Study

Management of hyperkalemia in the FIDELIO-DKD trial was at the investigator's discretion, following local clinical guidelines, except for the temporary discontinuation of study drug in patients with a serum $[K^+] > 5.5$ mmol/L. At baseline, 136 (2.4%) patients were on a potassium binder; most of these patients were treated with calcium or sodium polystyrene sulphonate. During the trial, 307 (10.9%) and 183 (6.5%) patients in the finerenone and placebo groups, respectively, started treatment with a potassium binder (Table S4 and Figure S6). Only 1 patient (in the placebo group) received dialysis whilst hospitalized for hyperkalemia during the study. In patients with investigator-reported, treatment-emergent, hyperkalemia-related AEs, the most frequent action reported by the investigator as having the highest impact to reduce serum $[K^+]$ was the temporary withdrawal of study drug, consistent with the protocol-recommended action (Table 2).

Efficacy Outcomes in Patient Subgroups According to Risk of Hyperkalemia

Prespecified subgroup analyses demonstrated that the effects of finerenone versus placebo on the primary composite kidney, key secondary composite CV, and all-cause mortality outcomes were similar among patients with low (< 4.8 mmol/L), mid (≥ 4.8 – 5.0 mmol/L), or high (> 5.0 mmol/L) serum $[K^+]$ at baseline and among patients with moderate-to-severe eGFR impairment at baseline (Figure S7).

Discussion

Patients in FIDELIO-DKD had a high intrinsic risk of hyperkalemia because of their advanced CKD, T2D, and treatment with optimized doses of an ACEi or ARB. This was reflected by the high incidence of hyperkalemia in the placebo arm during the study. Hyperkalemia (defined quantitatively by central laboratory assessment of serum $[K^+]$ measured at every study visit) was about 2-fold higher with finerenone than placebo, including across multiple patient

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3 subgroups. Notably, hyperkalemia was the only AE or serious AE to demonstrate excess
4 cases with finerenone; it was an expected side effect of MR antagonism,¹¹ and the kidney
5 and CV benefits of finerenone seen in the overall population were maintained in patients at
6 highest risk of hyperkalemia.⁷
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13 These analyses describe the risk factors that independently predicted the development of
14 hyperkalemia in FIDELIO-DKD, including baseline serum [K⁺], baseline eGFR, and baseline
15 UACR. Although lower eGFR (<45 mL/min/1.73 m²) and higher baseline potassium
16 concentration (>4.5 mmol/L) are well-established risk factors for hyperkalemia,^{9,12} it is also
17 the case that higher UACR is associated with increased hyperkalemia,¹³ although this
18 appears to be less widely recognized; in this analysis, a strong and robust relationship
19 emerged between higher UACR and subsequent occurrence of hyperkalemia. Unlike
20 previous studies that have found male sex and advanced age to be hyperkalemia risk
21 factors,¹³⁻¹⁵ we found the converse, and the reasons are unclear. Notably, optimizing RAS
22 inhibition before starting treatment with finerenone did not increase the risk of hyperkalemia,
23 perhaps because RAS inhibitor dosing was individualized during the run-in period (up-titrated
24 to the highest dose that each patient could safely tolerate). The use of diuretics and an
25 SGLT-2i may be prudent strategies to reduce the risk of hyperkalemia. However, because
26 few patients were treated with an SGLT-2i at baseline (partly because SGLT-2i use at the
27 time of the study was restricted to patients with higher eGFR values) these results should be
28 interpreted with caution.
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49 Short-term increases in serum [K⁺] after the start of treatment were predictive of subsequent
50 risk of hyperkalemia; this risk was shared between placebo and finerenone. However, for any
51 given increase in serum [K⁺] between baseline and month 4 versus no change, the increased
52 risk of hyperkalemia was smaller with finerenone than placebo. These findings may appear
53 counterintuitive but can be explained by the following considerations: finerenone is expected
54 to increase serum [K⁺] through MR antagonism, which may have triggered changes in
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3 management, such as finerenone treatment interruption and dose reduction, or adding other
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5 therapies (such as diuretics or potassium binders) that might mitigate the subsequent risk of
6
7 hyperkalemia.⁹ On the other hand, increases in serum $[K^+]$ provoked by placebo may reflect
8
9 processes in the kidney that reduce its ability to secrete potassium, such as acute kidney
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11 injury, tubulointerstitial inflammation, or obstruction¹⁶; these are less amenable to treatment
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13 interventions (evidence on the effectiveness of potassium binders and loop diuretics in an
14
15 acute setting are lacking) and are unaffected by reducing the dose of placebo.⁹
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20 Short-term decreases in eGFR after the start of treatment were associated with an increased
21
22 risk of hyperkalemia during the study, and the magnitude of the increased risk for any given
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24 reduction in eGFR versus no change in eGFR was smaller with finerenone than with
25
26 placebo. Provoked by natriuresis or modest blood pressure reduction, the decrease in eGFR
27
28 induced by finerenone is hemodynamic (in contrast to a tubular cause) and is less likely to
29
30 impair the ability to secrete potassium. Therefore, temporary treatment interruption and
31
32 finerenone dose reduction are likely to restore eGFR towards normal and normalize serum
33
34 $[K^+]$. On the other hand, short-term decreases in eGFR in patients receiving placebo may be
35
36 due to tubular factors or obstructive uropathy, which also impair the ability to secrete
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38 potassium,⁹ thus increasing the subsequent risk of hyperkalemia. Moreover, because
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40 finerenone slows eGFR decline versus placebo, this may reduce the risk of subsequent
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42 hyperkalemia.⁷
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47 Relative to the incidence of hyperkalemia in FIDELIO-DKD, a higher incidence was reported
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49 in trials using dual RAS inhibition.⁴⁻⁶ In VA NEPHRON-D, 32/724 (4.4%) patients in the
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51 losartan group, and 72/724 (9.9%) patients in the losartan plus lisinopril group experienced
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53 severe hyperkalemia (defined as serum $[K^+] >6.0$ mmol/L, or hyperkalemia requiring a visit to
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55 the emergency room, hospitalization, or dialysis). Thus, in the VA NEPHRON-D study, 18
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57 patients would have needed to have been prescribed dual RAS blockade for 1 patient to
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59 develop severe hyperkalemia.⁵ Similarly, looking at hyperkalemia events leading to
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3 permanent treatment discontinuation in ALTITUDE and ORIENT, a small number of patients
4 (45 and 26 patients, respectively) would have needed to be treated with dual RAS blockade
5 before 1 patient would have needed to stop treatment because of hyperkalemia.^{4,6} In
6
7 contrast, in FIDELIO-DKD, 71 patients would have needed to be prescribed finerenone
8 before 1 patient permanently stopped the drug.⁷ Furthermore, in FIDELIO-DKD, finerenone
9 significantly reduced the risk of the composite kidney and CV outcomes (by 18% and 14%,
10 respectively) compared with placebo, whereas the dual RAS-inhibitor studies failed to
11 demonstrate kidney or CV benefits.⁴⁻⁶
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22 A common comparator for a nonsteroidal MRA, albeit not indicated for patients with CKD, is
23 the steroidal MRA spironolactone. A *Cochrane Database Systematic* review of 27 small
24 studies including patients with CKD stages 1–4 with and without diabetes ($N=1549$) noted
25 that spironolactone plus an ACEi or ARB decreased albuminuria and blood pressure,
26 doubled the risk of hyperkalemia, and increased the risk of gynecomastia 5-fold, with
27 insufficient data to analyze benefits on clinical outcomes such as end-stage kidney disease.¹⁷
28 The active metabolites of spironolactone have a long half-life.^{11,18} In the AMBER study, which
29 included patients with CKD (eGFR 25–45 mL/min/1.73 m²) and resistant hypertension, an
30 exploratory analysis showed that 75% of patients still had detectable urinary metabolites of
31 spironolactone 2 weeks after stopping treatment. Moreover, approximately 2 in 3 patients
32 developed \geq mild hyperkalemia and approximately 1 in 4 patients had to discontinue
33 spironolactone because of hyperkalemia within 12 weeks. Even when given the
34 potassium-binding drug patiromer, over 30% of patients developed \geq mild hyperkalemia and
35 6.8% of patients stopped spironolactone because of hyperkalemia.¹⁹ These high rates of
36 hyperkalemia and discontinuation of spironolactone in AMBER suggest that the incidence of
37 hyperkalemia with finerenone may be lower than with spironolactone in comparable patient
38 populations. In addition, in a head-to-head phase 2 study in patients with heart failure with
39 reduced ejection fraction and CKD, the incidence of hyperkalemia was 11.1% with
40 spironolactone (25–50 mg od) compared with 4.8% with finerenone (10 mg od).²⁰ Once-daily
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3 oral administrations of 5 mg and 10 mg of finerenone were at least as effective as
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5 spironolactone (25 mg or 50 mg/day) in decreasing cardiorenal biomarker levels, but resulted
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7 in smaller increases in serum potassium, lower incidences of hyperkalemia and worsening
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9 renal function, and smaller reductions in systolic blood pressure.²⁰ These observations
10
11 suggest that some pharmacodynamic effects mediated by MRAs, including blood pressure
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13 control or serum potassium changes, are the consequence of a significant drug exposure
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15 over a long period (long half-life, area-under-the-curve driven), whereas others (e.g. anti-
16
17 inflammatory, anti-hypertrophic, and anti-fibrotic effects) are the consequences of relatively
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19 short drug exposure (short half-life, C_{max} driven) triggered by different signaling cascades.
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21 Strikingly, the rise in serum potassium with finerenone 5 mg twice daily was larger in
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23 comparison with finerenone 10 mg od, whereas reductions of N-terminal pro-B-type
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25 natriuretic peptide or albuminuria were similar.²⁰ This differential effect of once- versus twice-
26
27 daily dosing of finerenone illustrates the importance of consideration of both
28
29 pharmacokinetics and physiology when considering hyperkalemia rates. It is likely that the
30
31 low absolute risk of hyperkalemia with finerenone is because of its unique attributes: the
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33 short half-life of the drug, absence of active metabolites, balanced kidney–heart distribution
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35 (in rodent models) and the novel mechanism of action involving distinct blockade of the MR
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37 and different effects on subsequent gene expression.¹¹ Notably, because of the short half-life
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39 of finerenone (2–3 hours in patients with CKD) and lack of active metabolites,^{11,21} finerenone-
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41 associated hyperkalemia can be effectively managed by treatment interruption, as
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43 demonstrated in FIDELIO-DKD. It is important to highlight that these properties contrast with
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45 the long half-life and multiple active metabolites of spironolactone, as well as the fact that
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47 spironolactone has a kidney versus heart tissue distribution of approximately 6:1 (~1:1 for
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49 finerenone) in rodent models, and that spironolactone interacts with the MR in a different
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51 manner to finerenone.^{11,21}
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57 Esaxerenone is a potent and highly selective nonsteroidal MRA with a much longer half-life
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59 (~19 hours) than finerenone.²² In a patient population with less advanced CKD and T2D, 52

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3 weeks of treatment with esaxerenone led to discontinuation due to elevated serum [K⁺] in
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5 4.0% of patients compared with 0.4% of patients receiving placebo.^{23,24} Another steroidal
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7 MRA, eplerenone, which is more selective than spironolactone, approximately doubles the
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9 risk of hyperkalemia in patients with heart failure,^{25,26} and is contraindicated in patients with
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11 T2D and moderately elevated albuminuria without heart failure (in the USA).²⁷
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15 Results from the FIDELIO-DKD trial provide insights into requirements for serum [K⁺]
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17 monitoring in patients treated with finerenone. The earliest time point after which serum [K⁺]
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19 was measured was 1 month after treatment initiation. Very few patients developed
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21 hyperkalemia at this time: 86/2742 (3.1%) and 34/2730 (1.2%) patients in the finerenone and
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23 placebo groups, respectively. The second scheduled serum [K⁺] assessment was at month 4
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25 following treatment initiation, and at four monthly intervals thereafter. The frequency of
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27 potassium monitoring employed in FIDELIO-DKD was similar to the frequency of monitoring
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29 recommended for patients with CKD in the 2012 Kidney Disease: Improving Global
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31 Outcomes (KDIGO) guidelines (3–4 times a year for patients with UACR >300 mg/g and
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33 eGFR <60 mL/min/1.73 m², and 2–3 times a year for patients with UACR 30–300 mg/g and
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35 eGFR 15–59 mL/min/1.73 m²).³ Evidence from routine clinical practice suggests that
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37 physicians often intervene and reduce the dose of RAS inhibitors when serum [K⁺] rises
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39 above 5.0 mmol/L²⁸; in FIDELIO-DKD, RAS inhibitor dose reduction was not permitted and
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41 finerenone was continued with no dose adjustments in patients with a serum [K⁺] between
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43 5.0–5.5 mmol/L. It was only when serum [K⁺] rose to >5.5 mmol/L that finerenone was
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45 temporarily withheld. Treatment was resumed (at the 10 mg dose) when serum [K⁺] was
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47 ≤5.0 mmol/L. The occurrence of serum [K⁺] >5.5 or >6.0 mmol/L accumulated gradually over
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49 time and could occur months or years after starting finerenone. This may be related to two
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51 important determinants of hyperkalemia: declining kidney function and increasing serum [K⁺],
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53 or a combination of both.²⁹ Thus, potassium monitoring at each clinical follow-up visit would
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55 be a prudent strategy, in addition to both physicians and patients being aware of conditions
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57 or triggers that may precipitate a hyperkalemia event, such as medications (e.g.
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3 trimethoprim), acute illness, volume depletion, and acute kidney injury.^{29,30} The FIDELIO-
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5 DKD protocol has established a reliable potassium management algorithm, aligned to current
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7 guidelines,³ that may serve as a framework for use in clinical practice, taking into
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9 consideration patient characteristics (i.e. eGFR and baseline serum [K⁺]) that may increase
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11 their risk of hyperkalemia.
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16 In summary, these analyses from FIDELIO-DKD characterize the risk of hyperkalemia in
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18 patients with CKD and T2D, reporting that finerenone was associated with a low absolute risk
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20 of clinically relevant hyperkalemia, with only a small proportion of events having a clinical
21
22 impact. These analyses contribute to the understanding of how clinical characteristics,
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24 established risk factors, and treatment with finerenone may interact. Notably, elevated serum
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26 [K⁺] and lower eGFR when starting treatment with finerenone did not abrogate kidney or CV
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28 benefits of finerenone. These data provide a robust basis for incorporation of finerenone into
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30 clinical practice, with routine potassium monitoring for patients with CKD and T2D considered
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32 appropriate to manage the risk of hyperkalemia.
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Author Contributions

RA, AJ, SDA, GF, PR, LMR, BP, PK, and GB designed the study. CS performed the statistical analysis. RA wrote the first draft of the manuscript with input from RL and DW. All authors were involved in data interpretation, review, and writing of the manuscript, had full access to the data, and accept final responsibility for the decision to submit for publication.

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33
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35
36

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References

1. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al.: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001 doi: 10.1056/NEJMoa011161
2. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al.: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001 doi: 10.1056/NEJMoa011303
3. Kidney Disease: Improving Global Outcomes: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 3: 1–150, 2013
4. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al.: Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 367: 2204–2213, 2012 doi: 10.1056/NEJMoa1208799
5. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, et al.: Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 369: 1892–1903, 2013 doi: 10.1056/NEJMoa1303154
6. Imai E, Chan JC, Ito S, Yamasaki T, Kobayashi F, Haneda M, et al.: Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. *Diabetologia* 54: 2978–2986, 2011 doi: 10.1007/s00125-011-2325-z
7. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope L, Rossing P, et al.: Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 383: 2219–2229, 2020 doi: 10.1056/NEJMoa2025845
8. Terker AS, Ellison DH: Renal mineralocorticoid receptor and electrolyte homeostasis. *Am J Physiol Regul Integr Comp Physiol* 309: R1068–1070, 2015 doi: 10.1152/ajpregu.00135.2015
9. Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, et al.: Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 97: 42–61, 2020 doi: 10.1016/j.kint.2019.09.018
10. Filippatos G, Anker SD, Agarwal R, Pitt B, Ruilope LM, Rossing P, et al.: Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2

- 1
2
3 diabetes. *Circulation* 143: 540–552, 2021 doi:
4 10.1161/CIRCULATIONAHA.120.051898
5
6 11. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, et al.: Steroidal and
7 non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur*
8 *Heart J* 42: 152–161, 2021 doi: 10.1093/eurheartj/ehaa736
9
10 12. Lazich I, Bakris GL: Prediction and management of hyperkalemia across the
11 spectrum of chronic kidney disease. *Semin Nephrol* 34: 333–339, 2014 doi:
12 10.1016/j.semnephrol.2014.04.008
13
14 13. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, et al.:
15 Serum potassium and adverse outcomes across the range of kidney function: a CKD
16 Prognosis Consortium meta-analysis. *Eur Heart J* 39: 1535–1542, 2018 doi:
17 10.1093/eurheartj/ehy100
18
19 14. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, et al.: Incidence,
20 predictors, and outcomes related to hypo- and hyperkalemia in patients with severe
21 heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail* 7:
22 573–579, 2014 doi: 10.1161/circheartfailure.114.001104
23
24 15. Desai AS, Liu J, Pfeffer MA, Claggett B, Fleg J, Lewis EF, et al.: Incident
25 hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of
26 heart failure with preserved ejection fraction: analysis of the TOPCAT trial. *J Card Fail*
27 24: 313–320, 2018 doi: 10.1016/j.cardfail.2018.03.002
28
29 16. Palmer BF, Clegg DJ: Hyperkalemia across the continuum of kidney function. *Clin J*
30 *Am Soc Nephrol* 13: 155–157, 2018 doi: 10.2215/cjn.09340817
31
32 17. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GFM: Aldosterone antagonists
33 for preventing the progression of chronic kidney disease. *Cochrane Database Syst*
34 *Rev* 4: CD007004, 2014 doi: 10.1002/14651858.CD007004.pub3
35
36 18. Gardiner P, Schrode K, Quinlan D, Martin BK, Boreham DR, Rogers MS, et al.:
37 Spironolactone metabolism: steady-state serum levels of the sulfur-containing
38 metabolites. *J Clin Pharmacol* 29: 342–347, 1989 doi: 10.1002/j.1552-
39 4604.1989.tb03339.x
40
41 19. Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, et al.: Patiromer
42 versus placebo to enable spironolactone use in patients with resistant hypertension
43 and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-
44 controlled trial. *Lancet* 394: 1540–1550, 2019 doi: 10.1016/s0140-6736(19)32135-x
45
46 20. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, et al.: Safety
47 and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY
48 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney
49
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53
54
55
56
57
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59
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2
3 disease: a randomized, double-blind trial. *Eur Heart J* 34: 2453–2463, 2013 doi:
4 10.1093/eurheartj/eh187
5
6 21. Heinig R, Kimmeskamp-Kirschbaum N, Halabi A, Lentini S: Pharmacokinetics of the
7 novel nonsteroidal mineralocorticoid receptor antagonist finerenone (BAY 94-8862) in
8 individuals with renal impairment. *Clin Pharmacol Drug Dev* 5: 488–501, 2016 doi:
9 10.1002/cpdd.263
10
11 22. Arai K, Homma T, Morikawa Y, Ubukata N, Tsuruoka H, Aoki K, et al.:
12 Pharmacological profile of CS-3150, a novel, highly potent and selective non-steroidal
13 mineralocorticoid receptor antagonist. *Eur J Pharmacol* 761: 226–234, 2015 doi:
14 10.1016/j.ejphar.2015.06.015
15
16 23. Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y, et al.: Esaxerenone
17 (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN). *Clin J*
18 *Am Soc Nephrol* 15: 1715–1727, 2020 doi: 10.2215/CJN.06870520
19
20 24. Kario K, Ito S, Itoh H, Rakugi H, Okuda Y, Yoshimura M, et al.: Effect of the
21 nonsteroidal mineralocorticoid receptor blocker, esaxerenone, on nocturnal
22 hypertension: a post hoc analysis of the ESAX-HTN study. *Am J Hypertens* 34: 540-
23 551, 2021 doi: 10.1093/ajh/hpaa155
24
25 25. Ferreira JP, Abreu P, McMurray JJV, van Veldhuisen DJ, Swedberg K, Pocock SJ, et
26 al.: Renal function stratified dose comparisons of eplerenone versus placebo in the
27 EMPHASIS-HF trial. *Eur J Heart Fail* 21: 345-351, 2019 doi: 10.1002/ejhf.1400
28
29 26. Vukadinović D, Lavall D, Vukadinović AN, Pitt B, Wagenpfeil S, Böhm M: True rate of
30 mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled
31 trials: A meta-analysis. *Am Heart J* 188: 99–108, 2017 doi: 10.1016/j.ahj.2017.03.011
32
33 27. Pfizer: Inspra® (eplerenone) Prescribing Information, 2020. Available at:
34 <http://labeling.pfizer.com/ShowLabeling.aspx?id=599>. Accessed 1 April 2021
35
36 28. Linde C, Bakhai A, Furuland H, Evans M, McEwan P, Ayoubkhani D, et al.: Real-
37 world associations of renin-angiotensin-aldosterone system inhibitor dose,
38 hyperkalemia, and adverse clinical outcomes in a cohort of patients with new-onset
39 chronic kidney disease or heart failure in the United Kingdom. *J Am Heart Assoc* 8:
40 e012655, 2019 doi: 10.1161/jaha.119.012655
41
42 29. Hollander-Rodriguez JC, Calvert JF, Jr.: Hyperkalemia. *Am Fam Physician* 73: 283–
43 290, 2006
44
45 30. Kovesdy CP: Management of hyperkalaemia in chronic kidney disease. *Nat Rev*
46 *Nephrol* 10: 653–662, 2014 doi: 10.1038/nrneph.2014.168
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Table 1. Baseline demographics in patients with versus without any serum potassium concentration >5.5 mmol/L

Baseline demographics ^a	No serum [K ⁺] >5.5 mmol/L (n=4604)	Any serum [K ⁺] >5.5 mmol/L (n=1054)
Sex, male, n (%)	3279 (71.2)	694 (65.8)
Age, years, mean ± SD	65.81±9.02	64.45±9.09
Age category, n (%)		
<65 years	1879 (40.8)	493 (46.8)
65–74 years	1960 (42.6)	434 (41.2)
≥75 years	765 (16.6)	127 (12.0)
Serum [K ⁺], mmol/L, mean ± SD	4.31±0.43	4.65±0.48
Serum [K ⁺], mmol/L, n (%)		
≤4.1	1577 (34.3)	131 (12.4)
>4.1–≤4.5	1706 (37.1)	323 (30.6)
>4.5–≤4.8	878 (19.1)	274 (26.0)
>4.8–≤5.0	247 (5.4)	132 (12.5)
>5.0	196 (4.3)	194 (18.4)
eGFR, mL/min/1.73 m ² , mean ± SD	44.83±12.43	42.20±12.86
eGFR category, mL/min/1.73 m ² , n (%)		
<25	102 (2.2)	33 (3.1)
25–<45	2334 (50.7)	638 (60.5)
45–<60	1611 (35.0)	286 (27.1)
≥60	557 (12.1)	97 (9.2)
UACR, mg/g, median (IQR)	820.45 (439.79–1565.00)	956.94 (479.18–1917.93)
UACR category, mg/g, n (%)		
<30	18 (0.4)	5 (0.5)
30–<300	547 (11.9)	137 (13.0)
≥300	4038 (87.7)	912 (86.5)
eGFR 25–<45 mL/min/1.73 m ² and serum [K ⁺] >4.5 mmol/L, n (%)		
No	3897 (84.6)	699 (66.3)
Yes	707 (15.4)	355 (33.7)
Label-recommended dose of RASi, n (%)		
≤ minimum	1368 (29.7)	331 (31.4)
> minimum to < maximum	1125 (24.4)	263 (25.0)
≥ maximum	2096 (45.5)	458 (43.5)
Beta-blocker, n (%)	2405 (52.2)	560 (53.1)
Diuretic, n (%)	2677 (58.1)	527 (50.0)
Loop	1338 (29.1)	275 (26.1)
Thiazide	1146 (24.9)	205 (19.4)
Potassium binders, n (%)	91 (2.0)	45 (4.3)
Potassium supplements, n (%)	156 (3.4)	14 (1.3)
Glucose-lowering therapies, n (%)	4481 (97.3)	1027 (97.4)
SGLT-2i	240 (5.2)	19 (1.8)

Percentages are rounded to the nearest decimal place. eGFR, estimated glomerular filtration rate; IQR, interquartile range; [K⁺], potassium concentration; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

^aInformation on RASi dosing was missing in 15 patients without any serum [K⁺] >5.5 mmol/L and 2 patients with any serum [K⁺] >5.5 mmol/L.

Table 2. Management of investigator-reported hyperkalemia^a (actions reported by the investigator as having the highest impact on hyperkalemia^b)

Action, n (%)	Finerenone (n=2827)	Placebo (n=2833)
Drug withdrawn	64 (2.3)	25 (0.9)
Drug interrupted	310 (11.0)	146 (5.2)
Dose reduced	9 (0.3)	6 (0.2)
Dose not changed	127 (4.5)	74 (2.6)
Not applicable or unknown	6 (0.3)	4 (0.1)

^aIn total, 516 (18.3%) patients in the finerenone group and 255 (9.0%) patients in the placebo group had an investigator-reported hyperkalemia-related adverse event.

^bActions were considered in the following order: drug withdrawn, drug interrupted, dose reduced, dose not changed, and not applicable and unknown.

Figure Legend

Figure 1. Potassium management algorithm in FIDELIO-DKD. FIDELIO-DKD, FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; $[K^+]$, serum potassium concentration; od, once daily. ^aif estimated glomerular filtration rate is stable (i.e. $\leq 30\%$ decrease since last available measurement); ^buptitration visits were performed at 4 weeks ± 7 days after any treatment interruption >7 days and after any uptitration; ^cRegular study visits were scheduled at month 1, month 4, and every 4 months thereafter; ^dif treatment interruption ≤ 7 days.

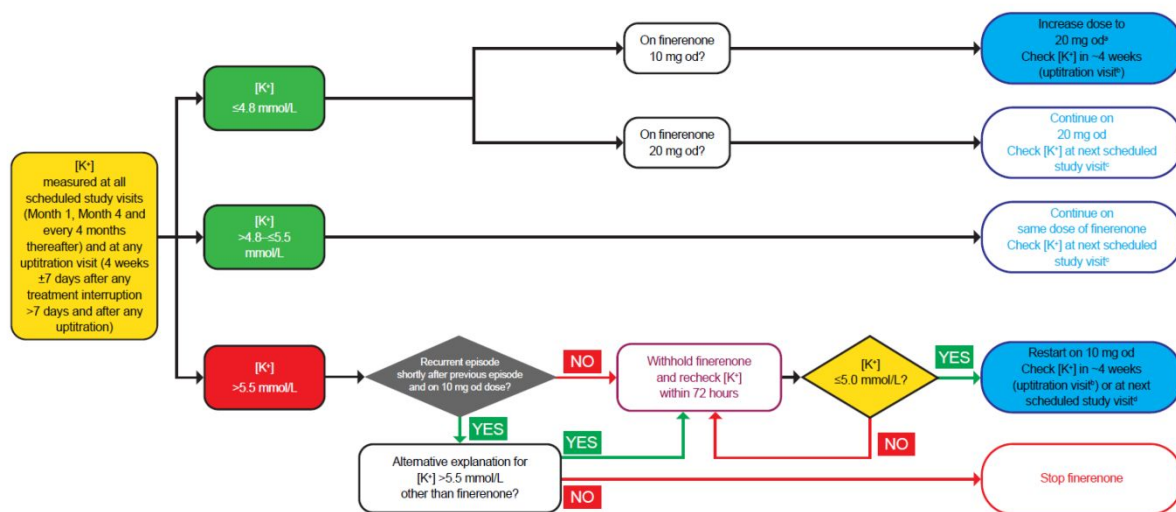


Figure 1. Potassium management algorithm in FIDELIO-DKD

Figure 2. Time to treatment-emergent serum potassium concentration (A) >5.5 mmol/L and (B) >6.0 mmol/L.

^aCumulative incidence calculated by Aalen–Johansen estimator using all-cause death as a competing risk; ^bincidence calculated as n/N over 2.6 years' median follow-up; ^cpatients at risk must have both a baseline and post-baseline treatment-emergent value and the baseline value must be below the threshold.

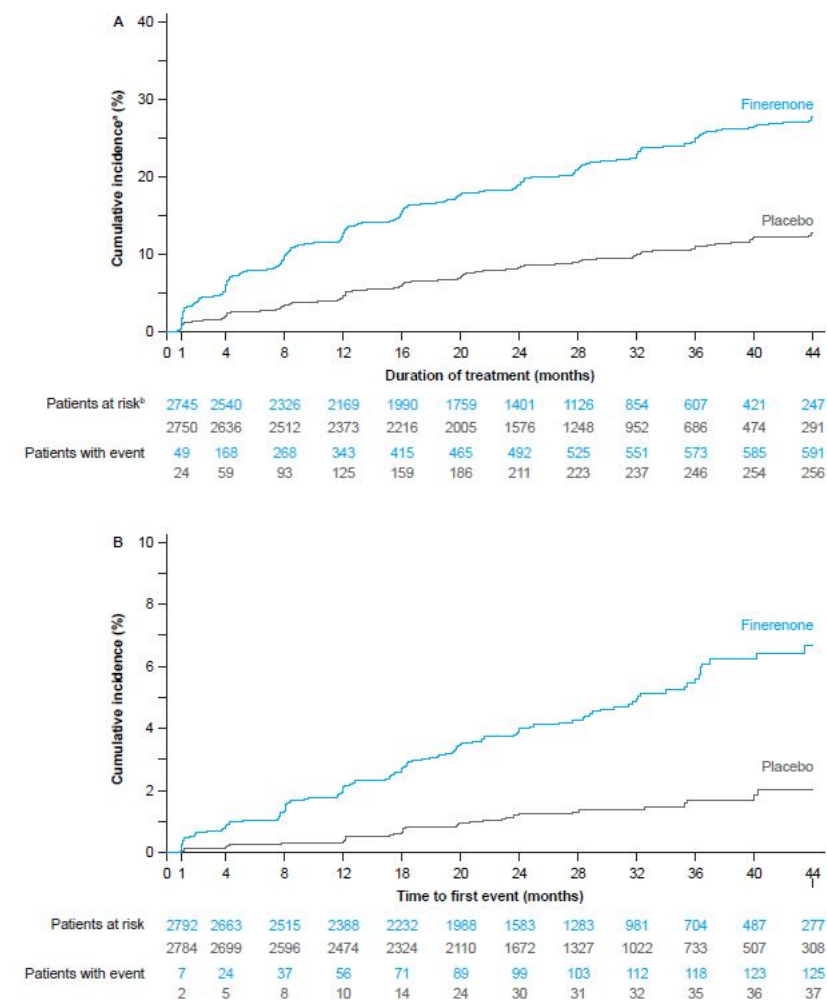


Figure 2. Time to treatment-emergent serum potassium concentration >5.5 mmol/L

Figure 3. Multivariate analysis of time to any serum potassium concentration >5.5 mmol/L. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio. ^aUACR is modelled as a continuous variable; 1 unit change in Log₂ UACR denotes doubling of UACR.

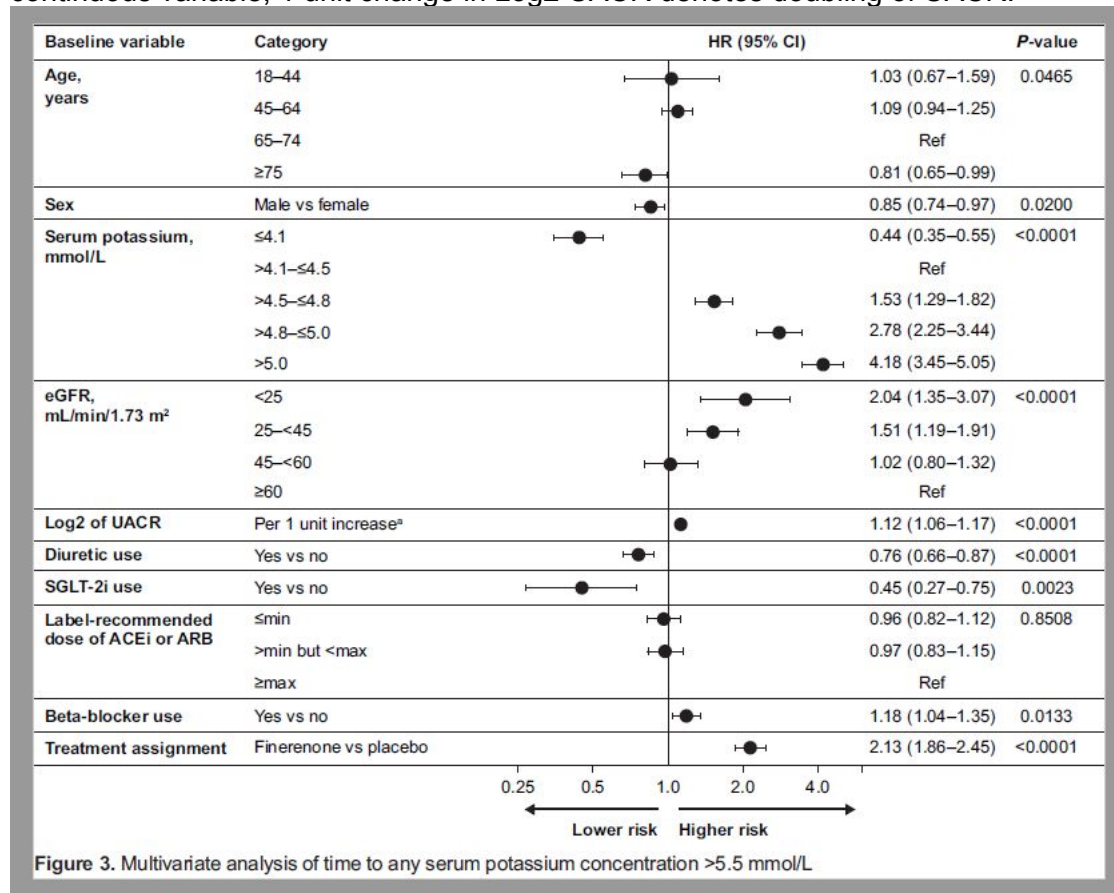
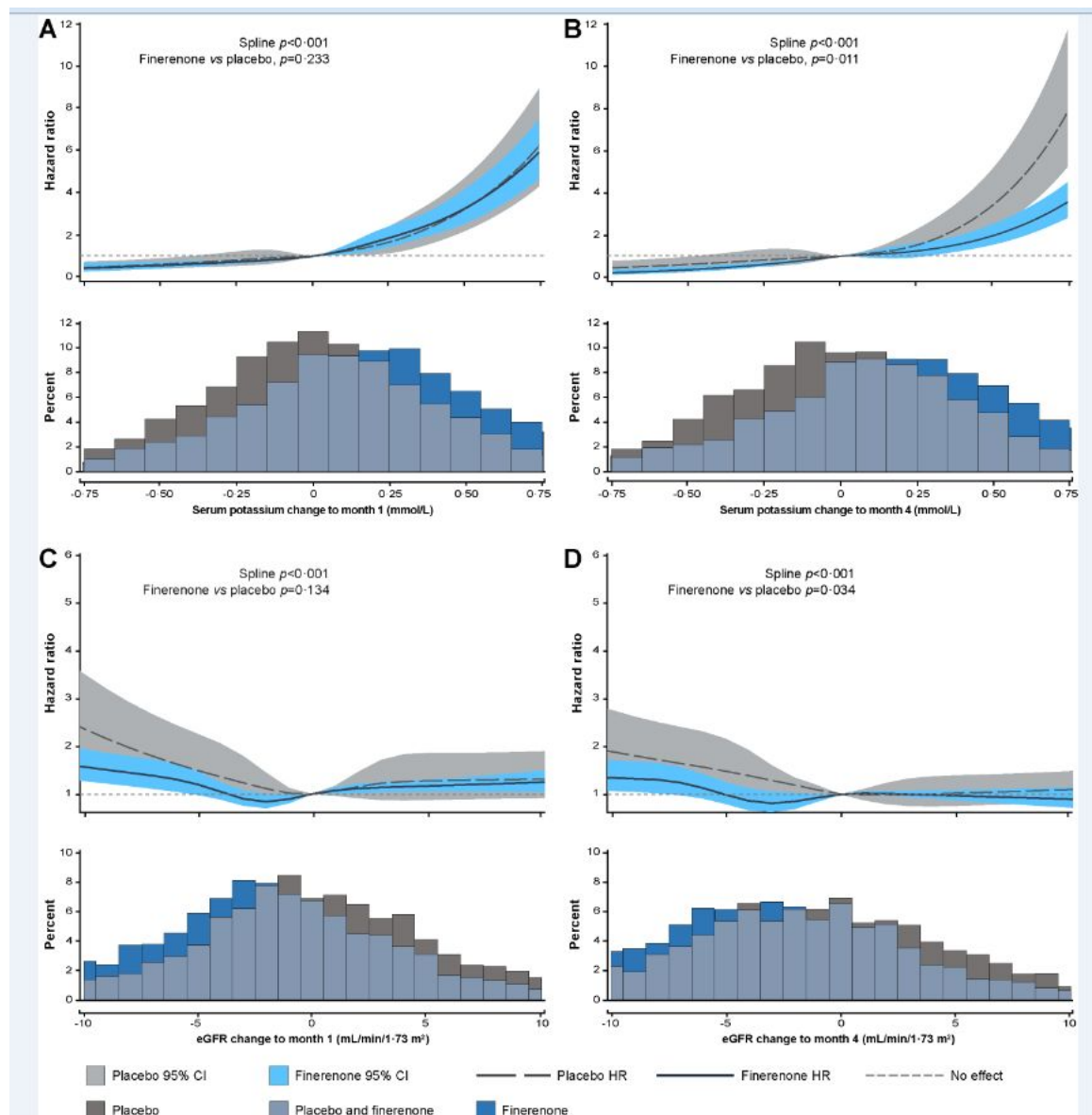


Figure 4. Short-term changes in serum potassium concentration and eGFR and the future risk of hyperkalemia (eGFR >5.5 mmol/L). (A) Changes in serum potassium concentration from baseline to month 1. (B) Changes in serum potassium concentration from baseline to month 4. (C) Changes in eGFR from baseline to month 1. (D) Changes in eGFR from baseline to month 4. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio



Hyperkalemia Risk with Finerenone: Results from the FIDELIO-DKD Trial

Rajiv Agarwal, Amer Joseph, Stefan D. Anker, Gerasimos Filippatos, Peter Rossing, Luis M. Ruilope, Bertram Pitt, Peter Kolkhof, Charlie Scott, Robert Lawatscheck, Dan Wilson, and George L. Bakris, on behalf of the FIDELIO-DKD Investigators.

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3 **Figure S5.** Impact of finerenone on hyperkalemia (serum potassium concentration >6.0
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9 **Figure S7.** Primary composite kidney, key secondary composite CV, and all-cause
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15 **Supplemental Appendix 1.** Full member list of the FIDELIO-DKD Investigators.
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Supplemental Tables

Table S1. Baseline demographics in patients with versus without any serum potassium concentration >5.5 mmol/L, by treatment group

Baseline demographics	No serum [K ⁺] >5.5 mmol/L		Any serum [K ⁺] >5.5 mmol/L	
	Finerenone (n=2151)	Placebo (n=2453)	Finerenone (n=676)	Placebo (n=378)
Sex, male, n (%)	1507 (70.1)	1772 (72.2)	442 (65.4)	252 (66.7)
Age, years, mean ± SD	65.64±8.95	65.96±9.08	64.87±8.87	63.70±9.44
Age category, n (%)				
<65 years	898 (41.7)	981 (40.0)	303 (44.8)	190 (50.3)
65–74 years	904 (42.0)	1056 (43.0)	291 (43.0)	143 (37.8)
≥75 years	349 (16.2)	416 (17.0)	82 (12.1)	45 (11.9)
Serum [K ⁺], mmol/L, mean ± SD	4.29±0.43	4.32±0.43	4.62±0.45	4.70±0.51
Serum [K ⁺], mmol/L, n (%)				
≤4.1	770 (35.8)	807 (32.9)	88 (13.0)	43 (11.4)
>4.1–≤4.5	808 (37.6)	898 (36.6)	213 (31.5)	110 (29.1)
>4.5–≤4.8	381 (17.7)	497 (20.3)	180 (26.6)	94 (24.9)
>4.8–≤5.0	107 (5.0)	140 (5.7)	84 (12.4)	48 (12.7)
>5.0	85 (4.0)	111 (4.5)	111 (16.4)	83 (22.0)

eGFR, mL/min/1.73 m ² , mean ± SD	45.03±12.54	44.66±12.34	42.22±12.30	42.17±13.82
eGFR category, mL/min/1.73 m ² , <i>n</i> (%)				
<25	48 (2.2)	54 (2.2)	18 (2.7)	15 (4.0)
25–<45	1060 (49.3)	1274 (51.9)	413 (61.1)	225 (59.5)
45–<60	782 (36.4)	829 (33.8)	189 (28.0)	97 (25.7)
≥60	261 (12.1)	296 (12.1)	56 (8.3)	41 (10.8)
UACR, mg/g, median (IQR)	820.42 (437.61–1551.41)	823.05 (442.76–1578.53)	866.85 (464.46–1803.19)	1161.43 (521.39–2236.54)
UACR category, mg/g, <i>n</i> (%)				
<30	8 (0.4)	10 (0.4)	3 (0.4)	2 (0.5)
30–<300	255 (11.9)	292 (11.9)	94 (13.9)	43 (11.4)
≥300	1887 (87.7)	2151 (87.7)	579 (85.7)	333 (88.1)
eGFR 25–<45 mL/min/1.73 m ² and serum [K ⁺] >4.5 mmol/L, <i>n</i> (%)				
No	1847 (85.9)	2050 (83.6)	447 (66.1)	252 (66.7)
Yes	304 (14.1)	403 (16.4)	229 (33.9)	126 (33.3)
History of CV disease, <i>n</i> (%)	986 (45.8)	1111 (45.3)	315 (46.6)	188 (49.7)

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Label-recommended dose of RASi, <i>n</i> (%) ^a				
≤ minimum	648 (30.1)	720 (29.4)	218 (32.2)	113 (29.9)
> minimum to < maximum	501 (23.3)	624 (25.4)	161 (23.8)	102 (27.0)
≥ maximum	994 (46.2)	1102 (44.9)	297 (43.9)	161 (42.6)
Beta-blocker, <i>n</i> (%)	1101 (51.2)	1304 (53.2)	359 (53.1)	201 (53.2)
Diuretic, <i>n</i> (%)				
Loop	610 (28.4)	728 (29.7)	176 (26.0)	99 (26.2)
Thiazide	563 (26.2)	583 (23.8)	134 (19.8)	71 (18.8)
Potassium binders, <i>n</i> (%)	43 (2.0)	48 (2.0)	27 (4.0)	18 (4.8)
Potassium supplements, <i>n</i> (%)	74 (3.4)	82 (3.3)	11 (1.6)	3 (0.8)
Glucose-lowering therapies, <i>n</i> (%)	2080 (96.7)	2401 (97.9)	661 (97.8)	366 (96.8)
SGLT-2i	111 (5.2)	129 (5.3)	13 (1.9)	6 (1.6)

Percentages are rounded to the nearest decimal place. CV, cardiovascular; eGFR, estimated glomerular filtration rate; IQR, interquartile range; [K⁺], potassium concentration; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SGLT-2i, sodium–glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

^aInformation on RASi dosing was missing in 15 patients without any serum [K⁺] >5.5 mmol/L (8 patients in the finerenone group and 7 patients in the placebo group) and 2 patients with any serum [K⁺] >5.5 mmol/L (in the finerenone group).

Table S2. Baseline demographics in patients with versus without any serum potassium concentration >6.0 mmol/L

Baseline demographics	No serum [K ⁺] >6.0 mmol/L (n=5430)	Any serum [K ⁺] >6.0 mmol/L (n=228)
Sex, male, n (%)	3831 (70.6)	142 (62.3)
Age, years, mean ± SD	65.64±9.02	63.63±9.69
Age category, n (%)		
<65 years	2262 (41.7)	110 (48.2)
65–74 years	2298 (42.3)	96 (42.1)
≥75 years	870 (16.0)	22 (9.6)
Serum [K ⁺], mmol/L, mean ± SD	4.36±0.45	4.65±0.57
Serum [K ⁺], mmol/L, n (%)		
≤4.1	1677 (30.9)	31 (13.6)
>4.1–≤4.5	1960 (36.1)	69 (30.3)
>4.5–≤4.8	1097 (20.2)	55 (24.1)
>4.8–≤5.0	350 (6.4)	29 (12.7)
>5.0	346 (6.4)	44 (19.3)
eGFR, mL/min/1.73 m ² , mean ± SD	44.52±12.53	40.22±12.58
eGFR category, mL/min/1.73 m ² , n (%)		
<25	122 (2.2)	13 (5.7)
25–<45	2826 (52.0)	146 (64.0)
45–<60	1847 (34.0)	50 (21.9)
≥60	635 (11.7)	19 (8.3)
UACR, mg/g, median (IQR)	839.87 (442.88–1608.10)	1082.77 (562.93–2072.66)
UACR category, mg/g, n (%)		
<30	21 (0.4)	2 (0.9)

30–<300	660 (12.2)	24 (10.5)
≥300	4748 (87.4)	202 (88.6)
eGFR 25–<45 mL/min/1.73 m ² and serum [K ⁺] >4.5 mmol/L, <i>n</i> (%)		
No	4443 (81.8)	153 (67.1)
Yes	987 (18.2)	75 (32.9)
Label-recommended dose of RASi, <i>n</i> (%) ^a		
≤ minimum	1622 (29.9)	77 (33.8)
> minimum to < maximum	1334 (24.6)	54 (23.7)
≥ maximum	2457 (45.2)	97 (42.5)
Beta-blocker, <i>n</i> (%)	2855 (52.6)	110 (48.2)
Diuretic, <i>n</i> (%)	3102 (57.1)	102 (44.7)
Loop	1560 (28.7)	53 (23.2)
Thiazide	1310 (24.1)	41 (18.0)
Potassium binders, <i>n</i> (%)	123 (2.3)	13 (5.7)
Potassium supplements, <i>n</i> (%)	164 (3.0)	6 (2.6)
Glucose-lowering therapies, <i>n</i> (%)	5284 (97.3)	224 (98.2)
SGLT-2i	257 (4.7)	2 (0.9)

Percentages are rounded to the nearest decimal place. eGFR, estimated glomerular filtration rate; IQR, interquartile range; [K⁺], potassium concentration; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

^aInformation on RASi dosing was missing in 17 patients without any serum [K⁺] >6.0 mmol/L.

Table S3. Baseline demographics in patients with versus without any serum potassium concentration >6.0 mmol/L, by treatment group

Baseline demographics	No serum [K ⁺] >6.0 mmol/L		Any serum [K ⁺] >6.0 mmol/L	
	Finerenone (n=2680)	Placebo (n=2750)	Finerenone (n=147)	Placebo (n=81)
Sex, male, n (%)	1858 (69.3)	1973 (71.7)	91 (61.9)	51 (63.0)
Age, years, mean ± SD	65.48±8.91	65.79±9.12	64.90±9.51	61.32±9.64
Age category, n (%)				
<65 years	1135 (42.4)	1127 (41.0)	66 (44.9)	44 (54.3)
65–74 years	1133 (42.3)	1165 (42.4)	62 (42.2)	34 (42.0)
≥75 years	412 (15.4)	458 (16.7)	19 (12.9)	3 (3.7)
Serum [K ⁺], mmol/L, mean ± SD	4.36±0.45	4.36±0.45	4.62±0.50	4.71±0.69
Serum [K ⁺], mmol/L, n (%)				
≤4.1	839 (31.3)	838 (30.5)	19 (12.9)	12 (14.8)
>4.1–≤4.5	973 (36.3)	987 (35.9)	48 (32.7)	21 (25.9)
>4.5–≤4.8	526 (19.6)	571 (20.8)	35 (23.8)	20 (24.7)
>4.8–≤5.0	170 (6.3)	180 (6.5)	21 (14.3)	8 (9.9)
>5.0	172 (6.4)	174 (6.3)	24 (16.3)	20 (24.7)
eGFR, mL/min/1.73 m ² , mean ± SD	44.62±12.55	44.41±12.50	39.51±11.19	41.51±14.75

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eGFR category, mL/min/1.73 m ² , <i>n</i> (%)				
<25	57 (2.1)	65 (2.4)	9 (6.1)	4 (4.9)
25–<45	1376 (51.3)	1450 (52.7)	97 (66.0)	49 (60.5)
45–<60	938 (35.0)	909 (33.1)	33 (22.4)	17 (21.0)
≥60	309 (11.5)	326 (11.9)	8 (5.4)	11 (13.6)
UACR, mg/g, median (IQR)	818.57 (438.43–1593.89)	860.60 (447.76–1617.35)	1069.76 (558.44–2046.04)	1255.60 (637.20–2088.09)
UACR category, mg/g, <i>n</i> (%)				
<30	10 (0.4)	11 (0.4)	1 (0.7)	1 (1.2)
30–<300	333 (12.4)	327 (11.9)	16 (10.9)	8 (9.9)
≥300	2336 (87.2)	2412 (87.7)	130 (88.4)	72 (88.9)
eGFR 25–<45 mL/min/1.73 m ² and serum [K ⁺] >4.5 mmol/L, <i>n</i> (%)				
No	2197 (82.0)	2246 (81.7)	97 (66.0)	56 (69.1)
Yes	483 (18.0)	504 (18.3)	50 (34.0)	25 (30.9)
History of CV disease, <i>n</i> (%)	1237 (46.2)	1257 (45.7)	64 (43.5)	42 (51.9)
Label-recommended dose of RASi, <i>n</i> (%) ^a				

≤ minimum	815 (30.4)	807 (29.3)	51 (34.7)	26 (32.1)
> minimum to < maximum	628 (23.4)	706 (25.7)	34 (23.1)	20 (24.7)
≥ maximum	1229 (45.9)	1228 (44.7)	62 (42.2)	35 (43.2)
Beta-blocker, <i>n</i> (%)	1389 (51.8)	1466 (53.3)	71 (48.3)	39 (48.1)
Diuretic, <i>n</i> (%)	1509 (56.3)	1593 (57.9)	65 (44.2)	37 (45.7)
Loop	754 (28.1)	806 (29.3)	32 (21.8)	21 (25.9)
Thiazide	668 (24.9)	642 (23.3)	29 (19.7)	12 (14.8)
Potassium binders, <i>n</i> (%)	63 (2.4)	60 (2.2)	7 (4.8)	6 (7.4)
Potassium supplements, <i>n</i> (%)	81 (3.0)	83 (3.0)	4 (2.7)	2 (2.5)
Glucose-lowering therapies, <i>n</i> (%)	2596 (96.9)	2688 (97.7)	145 (98.6)	79 (97.5)
SGLT-2i	123 (4.6)	134 (4.9)	1 (0.7)	1 (1.2)

Percentages are rounded to the nearest decimal place. CV, cardiovascular; eGFR, estimated glomerular filtration rate; IQR, interquartile range; [K⁺], potassium concentration; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

^aInformation on RASi dosing was missing in 17 patients without any serum [K⁺] >6.0 mmol/L (8 patients in the finerenone group and 9 patients in the placebo group).

Table S4. Use of potassium binders at baseline and during the FIDELIO-DKD trial

	Finerenone (n=2827)	Placebo (n=2831)	Total (N=5558)
Patients receiving a potassium binder at baseline, <i>n</i> (%)	70 (2.5)	66 (2.3)	136 (2.4)
Calcium polystyrene sulphonate	51 (1.8)	40 (1.4)	91 (1.6)
Sodium polystyrene sulphonate	17 (0.6)	24 (0.8)	41 (0.7)
Patiromer	2 (<0.1)	2 (<0.1)	4 (<0.1)
Patients receiving a potassium binder at any point during the trial, <i>n</i> (%)	307 (10.9)	183 (6.5)	490 (8.7)
Calcium polystyrene sulphonate	154 (5.4)	102 (3.6)	256 (4.5)
Sodium polystyrene sulphonate	149 (5.3)	80 (2.8)	229 (4.0)
Patiromer	18 (0.6)	9 (0.3)	27 (0.5)
Sodium zirconium cyclosilicate	9 (0.3)	5 (0.2)	14 (0.2)

FIDELIO-DKD, Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease

Supplemental Figures

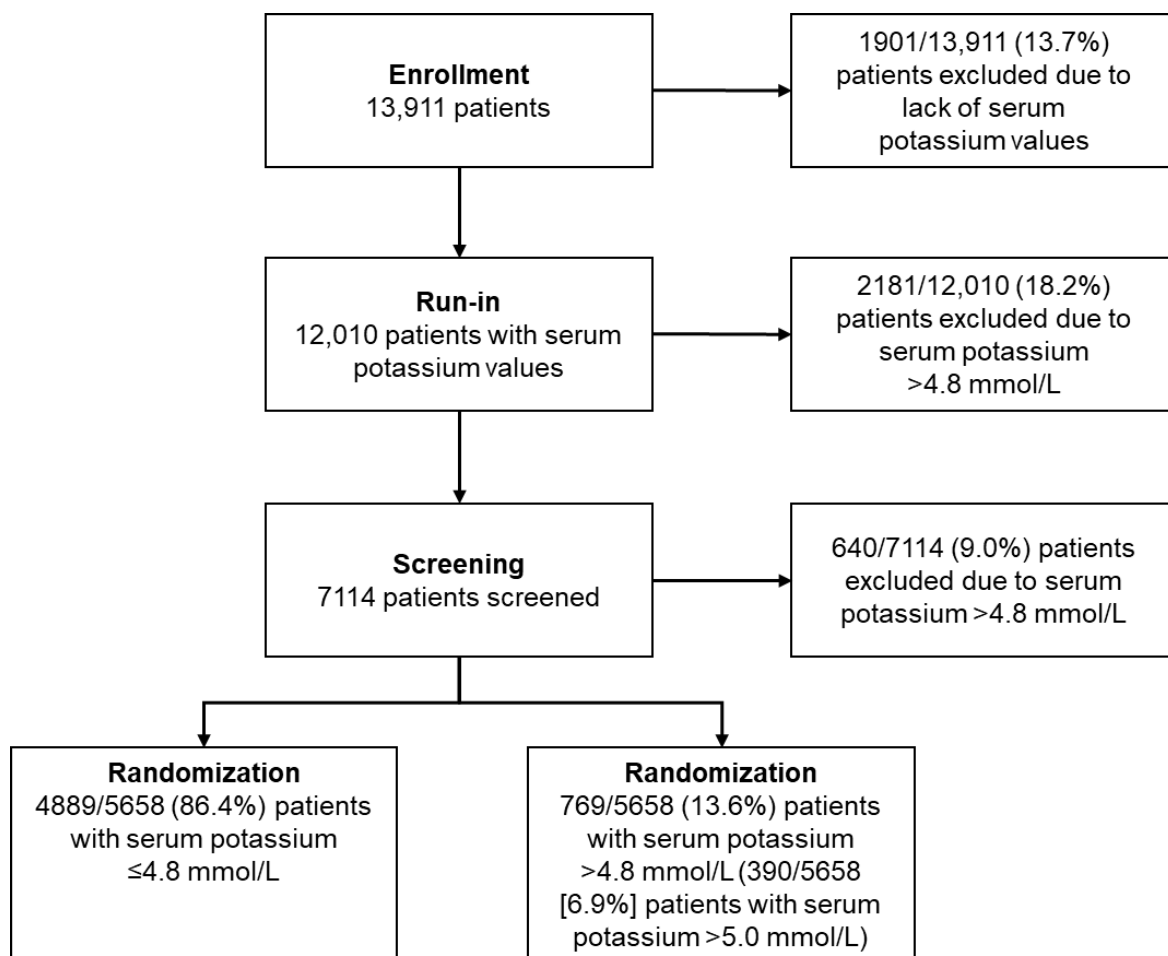


Figure S1. Flow of patients through the study from enrollment to randomization based on inclusion/exclusion related to serum potassium measurements.

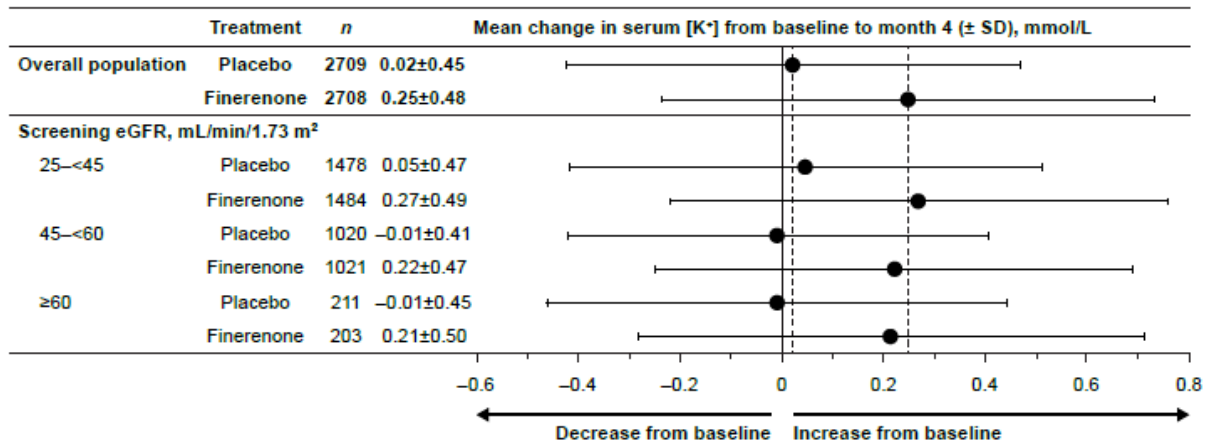


Figure S2. Mean change in serum potassium concentration from baseline to month 4 in the overall population and by eGFR category at the screening visit. eGFR, estimated glomerular filtration rate; SD, standard deviation.

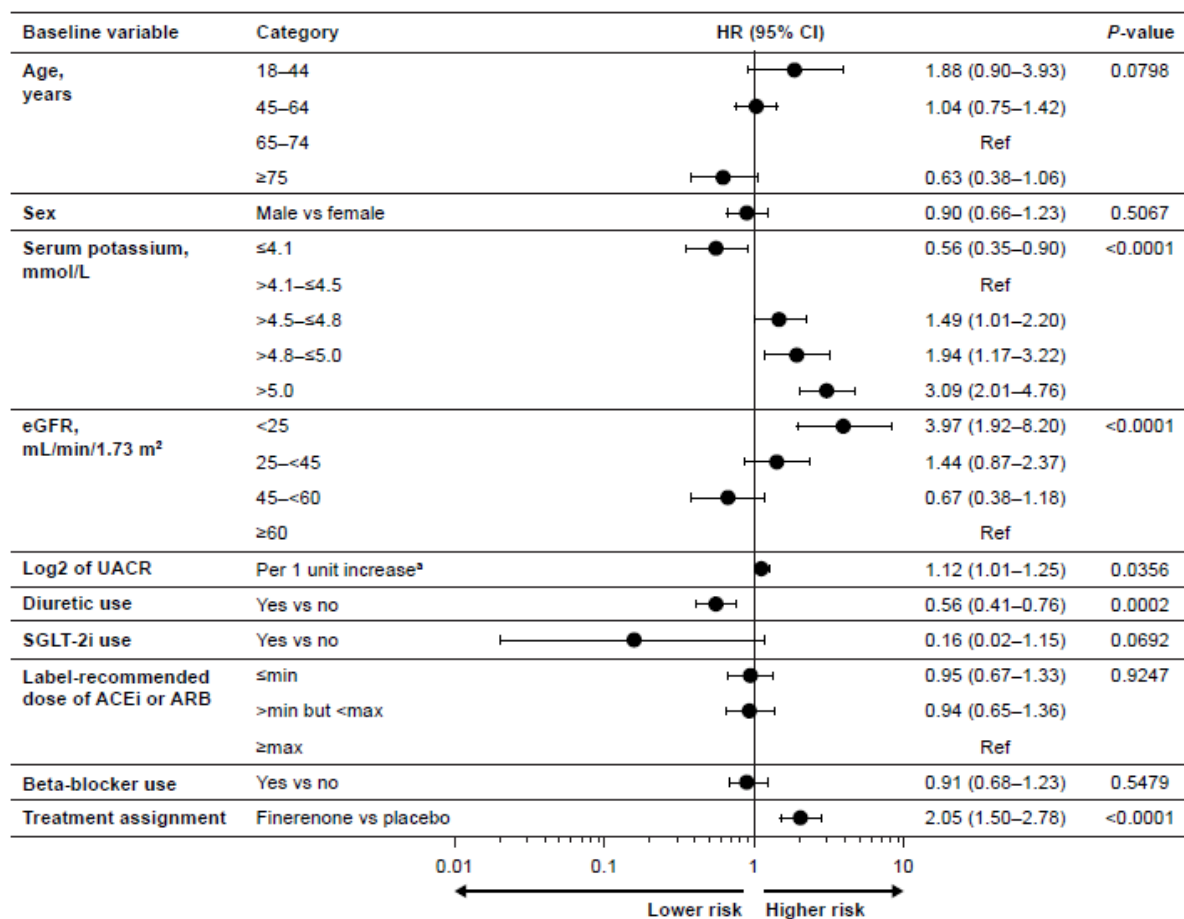


Figure S3. Multivariate analysis of time to any serum potassium concentration >6.0 mmol/L.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio. ^aUACR is modelled as a continuous variable; 1 unit change in Log₂ UACR denotes doubling of UACR.

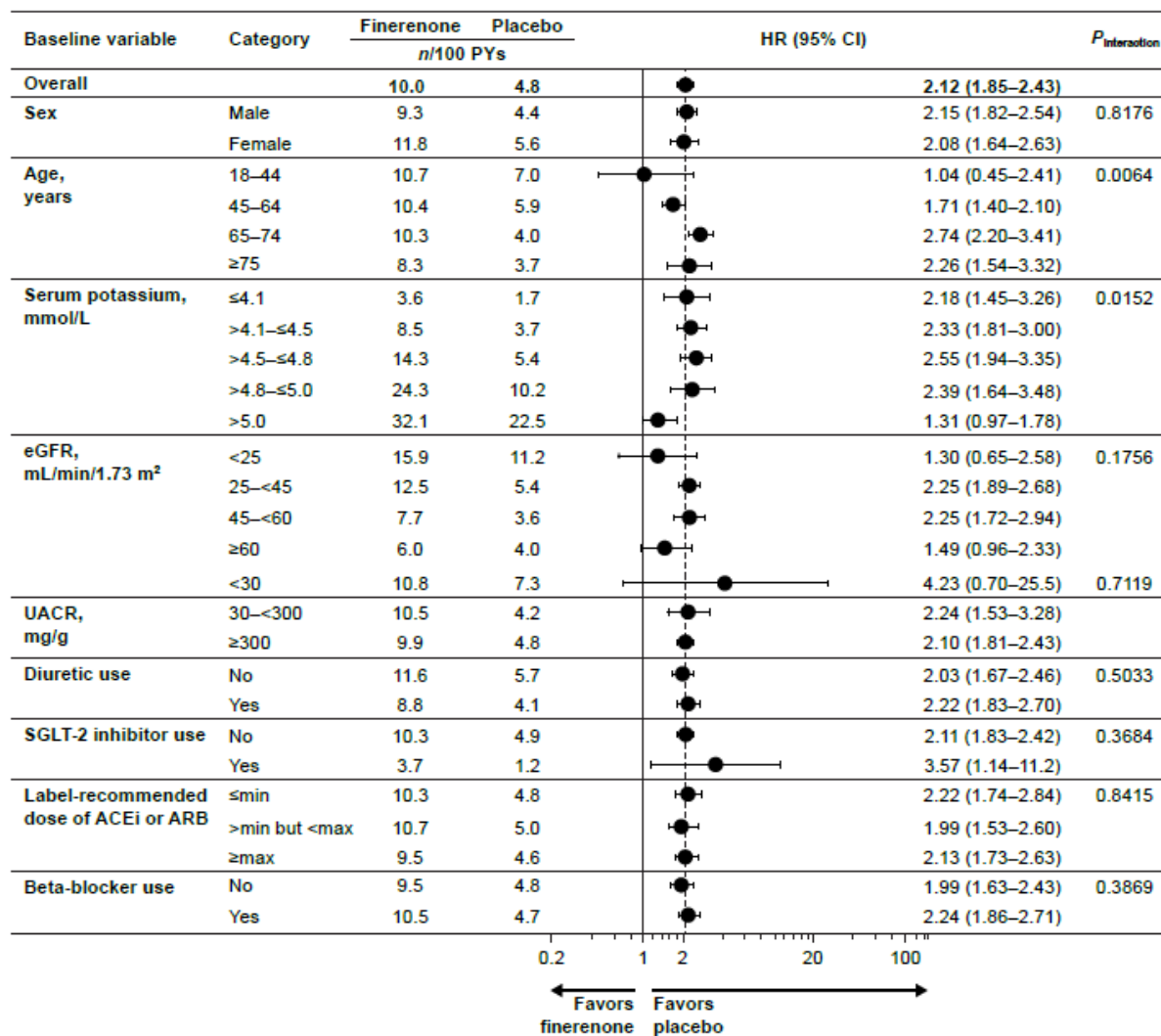


Figure S4. Impact of finerenone on hyperkalemia risk (serum potassium concentration >5.5 mmol/L) in patient subgroups. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-year; SGLT-2, sodium-glucose co-transporter-2; UACR, urine albumin-to-creatinine ratio.

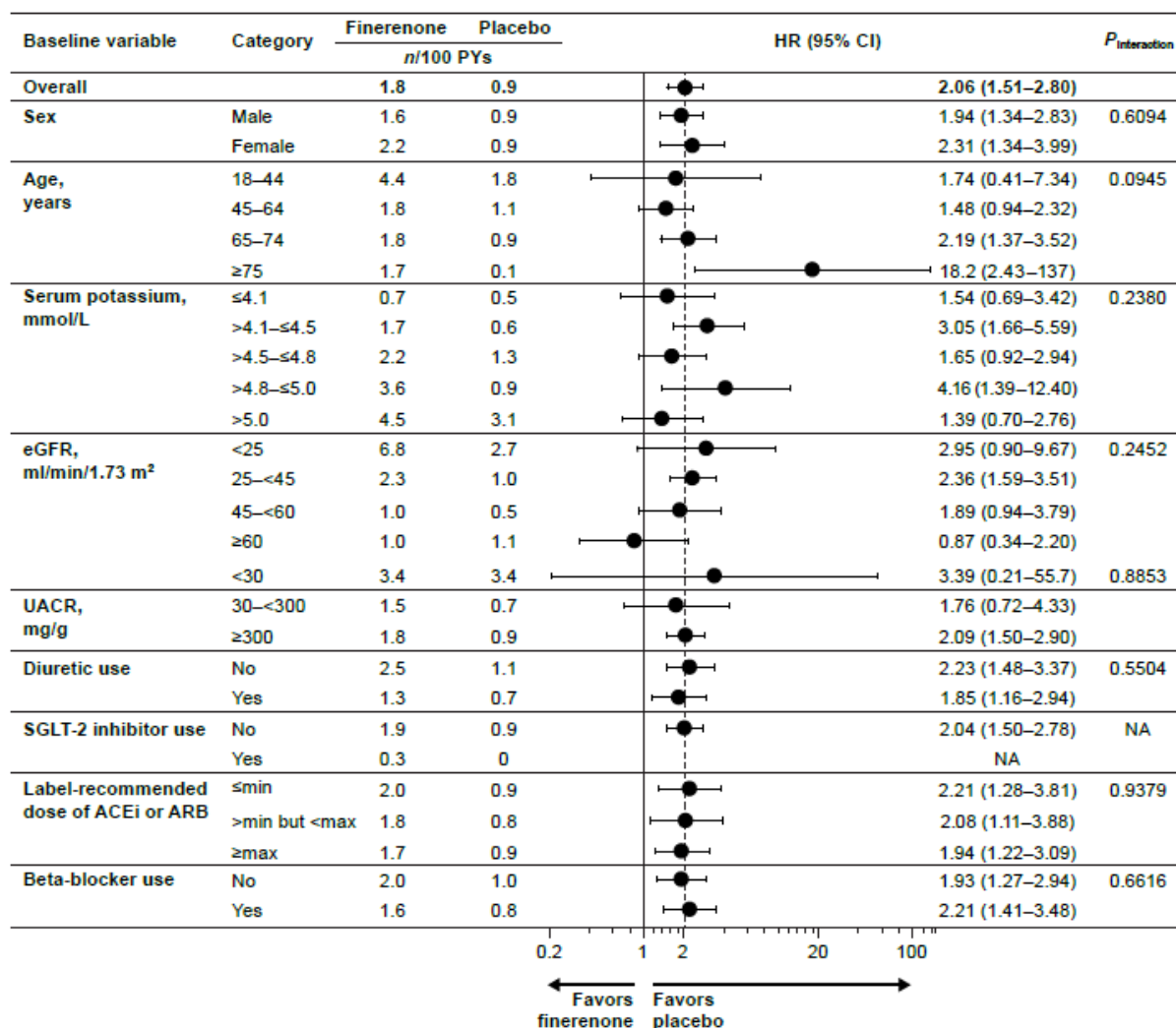


Figure S5. Impact of finerenone on hyperkalemia (serum potassium concentration >6.0 mmol/L) in patient subgroups. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-year; SGLT-2, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

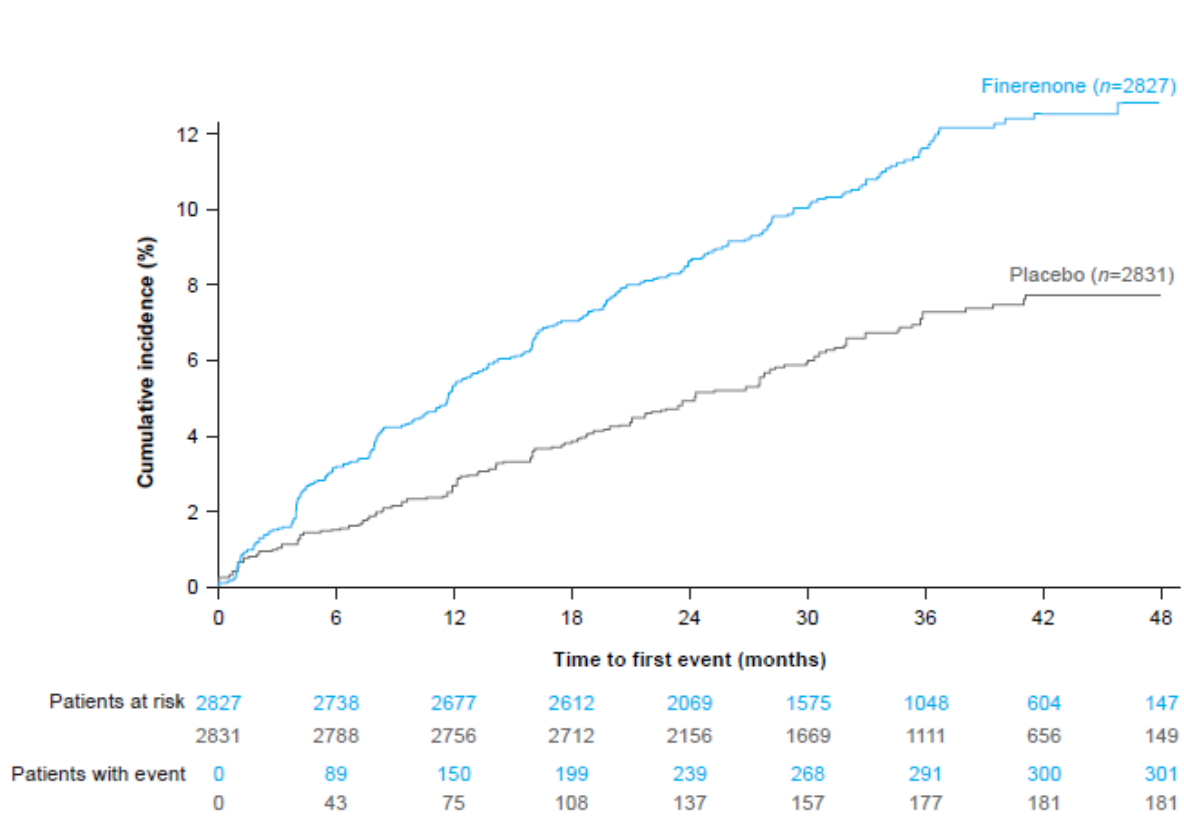


Figure S6. Time to first use of potassium binders.

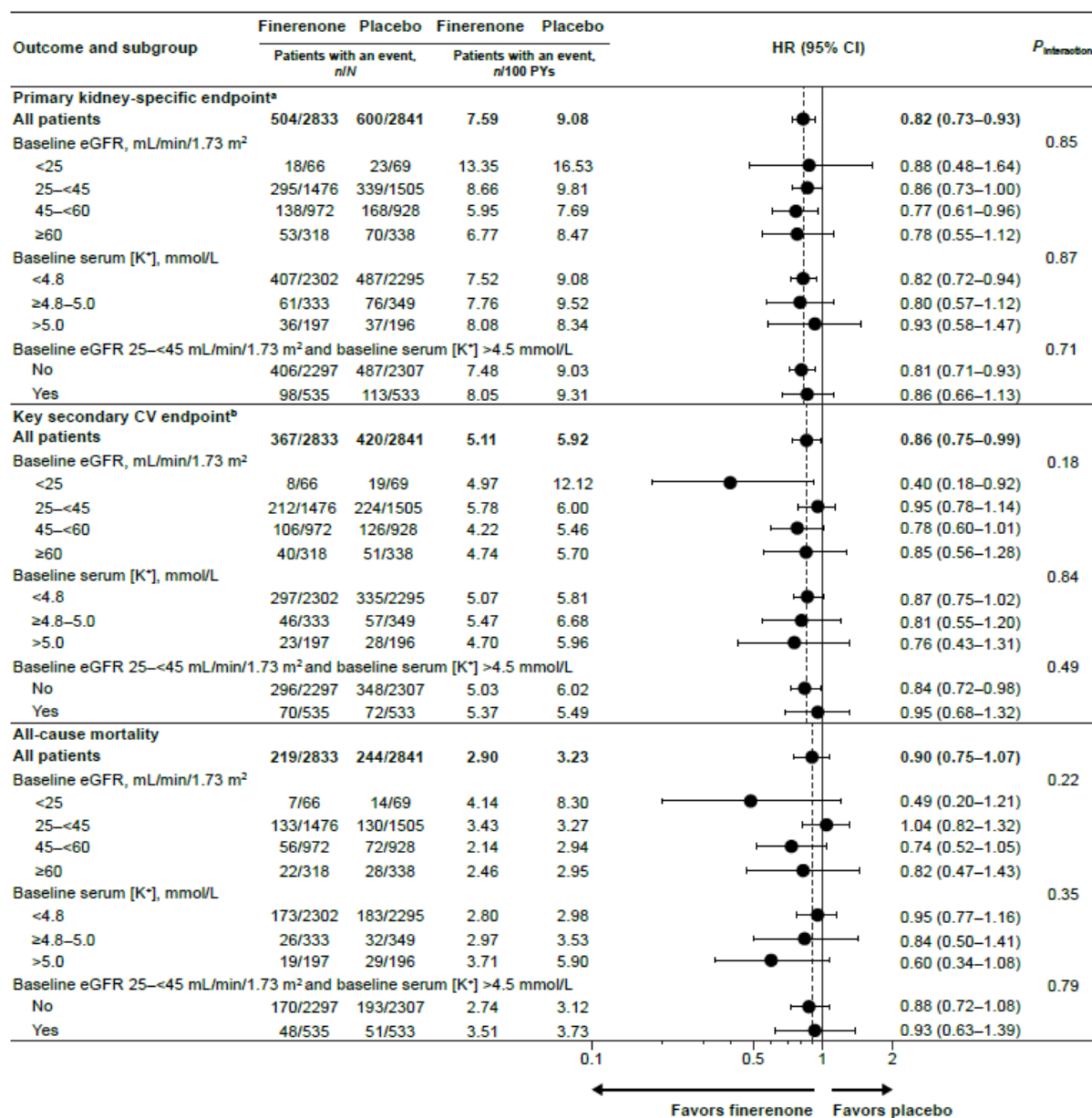


Figure S7. Primary composite kidney, key secondary composite CV, and all-cause mortality outcomes in patient subgroups at highest risk of hyperkalemia. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; [K⁺], potassium concentration; MI, myocardial infarction; PY, patient-year. ^aTime to first onset of kidney failure, a sustained ≥40% decrease in eGFR from baseline over ≥4 weeks, or renal death; ^btime of first onset of CV death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for heart failure.

Supplemental Appendix 1. Full member list of the FIDELIO-DKD

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31 Dong-Jin Oh, Junbeom Park, Seok Joon Shin, Su-Ah Sung, Jae Myung Yu

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34 **Spain:** Irene Agraz, Francisco Javier Ampudia, Hanane Bouarich, Francesca Calero,
35 Cristina Castro, Secundino Cigarrán Guldris, Josep Cruzado Garrit, Fernando de Álvaro,
36 Josep Galcerán, Olga González Albarrán, Julio Hernández Jaras, Meritxell Ibernón,
37 Francisco Martínez Deben, M^a Dolores Martínez Esteban, José María Pascual Izuel, Judith
38 Martins, Juan Mediavilla, Alfredo Michán, Julio Pascual Santos, Esteban Poch, Manuel
39 Polaina Rusillo, Carlos Sánchez Juan, Rafael Santamaría Olmo, José Julián Segura de la
40 Morena, Alfonso Soto, Maribel Troya

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43 **Sweden:** Annette Bruchfeld, Dan Curiac, Ken Eliasson, Malin Frank, Gregor Guron, Olof
44 Hellberg, Margareta Hellgren, Hans Larnefeldt, Carl-Johan Lindholm, Magnus Löndahl, Erik
45 Rein-Hedin, Inga Soveri, Jonas Spaak, Bengt-Olov Tengmark

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48 **Switzerland:** Daniel Ackermann, Stefan Bilz, Michel Burnier, Christian Forster, Stefan
49 Kalbermatter, Andreas Kistler, Antoinette Pechère-Bertschi, Bernd Schultes

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52 **Taiwan:** Chiz-Tzung Chang, Cheng-Chieh Hung, Ju-Ying Jiang, Chien-Te Lee, Shuei-Liong
53 Lin, Der-Cherng Tarng, Shih-Te Tu, Mai-Szu Wu, Ming-Ju Wu

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56 **Thailand:** Chaicharn Deerochanawong, Chagriya Kitiyakara, Vuddhidej Ophascharoensuk,
57 Chatlert Pongchaiyakul, Bancha Satirapoj

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3 **Turkey:** Necmi Eren, Ibrahim Gul, Okan Gulel, Ismail Kocyigit, Abdulbaki Kumbasar, Idris
4 Sahin, Ramazan Sari, Burak Sayin, Talat Tavli, Sedat Ustundag, Yavuz Yenicerioglu

5
6 **Ukraine:** Iryna Bondarets, Volodymyr Botsyurko, Viktoriia Chernikova, Oleksandra Donets,
7 Ivan Fushtey, Mariia Grachova, Anna Isayeva, Dmytro Kogut, Julia Komisarenko, Nonna
8 Kravchun, Kateryna Malyar, Borys Mankovsky, Liliya Martynyuk, Vitaliy Maslyanko, Halyna
9 Myshanych, Larysa Pererva, Nataliia Pertseva, Oleksandr Serhiyenko, Ivan Smirnov, Liubov
10 Sokolova, Vasyl Stryzhak, Maryna Vlasenko

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12 **United Kingdom:** Ahmad AbouSaleh, Jonathan Barratt, Cuong Dang, Hassan Kahal, Adam
13 Kirk, Anne Kilvert, Sui Phi Kon, Kieran McCafferty, Dipesh Patel, Sam Rice, Arutchelvam
14 Vijayaraman, Yuk-ki Wong, Martin Gibson, Mona Wahba, Reza Zaidi

15
16 **United States:** Idalia Acosta, Atoya Adams, Sharon Adler, Dilawar Ajani, Slamati Ali, Radica
17 Alicic, Amer Al-Karadsheh, Sreedhara Alla, D. Allison, Nabil Andrawis, Ahmed Arif, Ahmed
18 Awad, Masoud Azizad, Michael Bahrami, Shweta Bansal, Steven Barag, Ahmad Barakzoy,
19 Mark Barney, Joshua Barzilay, Khalid Bashir, Jose Bautista, Srinivasan Beddhu, Diogo Belo,
20 Sabrina Benjamin, Ramin Berenji, Anuj Bhargava, Jose Birriel, Stephen Brietzke, Frank
21 Brosius, Osvaldo Brusco, Anna Burgner, Robert Busch, Rafael Canadas, Maria Caramori,
22 Jose Cardona, Christopher Case, Humberto Cruz, Ramprasad Dandillaya, Dalia Dawoud,
23 Zia Din, Bradley Dixon, Ankur Doshi, James Drakakis, Mahfouz El Shahawy, Ashraf El-
24 Meanawy, Mohammed El-Shahawy, John Evans, George Fadda, Umar Farooq, Roland
25 Fernando, Raymond Fink, Brian First, David Fitz-Patrick, John Flack, Patrick Fluck, Leon
26 Fogelfeld, Vivian Fonseca, Juan Frias, Claude Galphin, Luis Garcia-Mayol, Gary Goldstein,
27 Edgar Gonzalez, Francisco Gonzalez-Abreu, Ashwini Gore, David Grant, Violet Habwe,
28 Maxine Hamilton, Jamal Hammoud, Stuart Handelsman, Israel Hartman, Glenn Heigerick,
29 Andrew Henry, German Hernandez, Carlos Hernandez-Cassis, Carlos Herrera, Joachim
30 Hertel, Wenyu Huang, Rogelio Iglesias, Ali Iranmanesh, Timothy Jackson, Mahendra Jain,
31 Kenneth Jamerson, Karen Johnson, Eric Judd, Joshua Kaplan, Zeid Kayali, Bobby Khan,
32 Muhammad Khan, Sourabh Kharait, M. Sue Kirkman, Nelson Kopyt, Wayne Kotzker, Csaba
33 Kovesdy, Camil Kreit, Arvind Krishna, Saeed Kronfli, Keung Lee, Derek LeJeune, Brenda
34 Lemus, Carlos Leon-Forero, Douglas Linfert, Henry Lora, Alexander Lurie, Geetha
35 Maddukuri, Alexander Magno, Louis Maletz, Sreedhar Mandayam, Mariana Markell, Ronald
36 Mayfield, Caroline Mbogua, Dierdre McMullen, Carl Meisner, Stephen Minton, Bharat
37 Mocherla, Rajesh Mohandas, Manuel Montero, Moustafa Moustafa, Salil Nadkarni, Samer
38 Nakhle, Jesus Navarro, Nilda Neyra, Romanita Nica, Philip Nicol, Paul Norwood, Visal
39 Numrungroad, Richard O' Donovan, A. Odugbesan, Jorge Paoli-Bruno, Samir Parikh,
40 Rakesh Patel, Aldo Peixoto, Pablo Pergola, Alan Perlman, Karlton Pettis, Roberto Pisoni,
41 Mirela Ponduchi, Jorge Posada, Sharma Prabhakar, Jai Radhakrishnan, Mahboob Rahman,
42 Rupesh Raina, Anjay Rastogi, Efrain Reisin, Marc Rendell, David Robertson, Michael Rocco,
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3 Hugo Romeu, Sylvia Rosas, Jack Rosenfeld, Dennis Ross, Jeffrey Rothman, Lance
4 Rudolph, Yusuf Ruhullah, Gary Ruoff, Jeffrey Ryu, Mandeep Sahani, Ramin Sam, Garfield
5 Samuels, William Sanchez, Vladimir Santos, Scott Satko, Sanjeev Saxena, David Scott,
6 Gilberto Seco, Melvin Seek, Harvey Serota, Tariq Shafi, Nauman Shahid, Michael Shanik,
7 Santosh Sharma, Arjun Sinha, James Smelser, Mark Smith, Kyaw Soe, Richard Solomon,
8 Eugene Soroka, Joseph Soufer, Bruce Spinowitz, Leslie Spry, Rosa Suarez, Bala
9 Subramanian, Harold Szerlip, Aparna Tamirisa, Stephen Thomson, Tuan-Huy Tran, Richard
10 Treger, Gretel Trullenque, Thomas Turk, Guillermo Umpierrez, Daniel Urbach, Martin
11 Valdes, Shujauddin Valika, Damaris Vega, Peter Weissman, Adam Whaley-Connell,
12 Jonathan Winston, Jonathan Wise, Alan Wynne, Steven Zeig
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14 **Vietnam:** Phuong Chu, Lam Van Hoang, Tran Khanh, Nguyen Thi Phi Nga, Pham Nguyen
15 Son, Lan Phuong Tran.
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