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

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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 <i>post hoc</i> safety analysis defined hyperkalemia as â‰¥mild or â‰¥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 Aalenâ€“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 â‰¥mild hyperkalemia had the study drug withheld until serum potassium was â‰¤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 yearsâ€™ median follow-up, 597/2785 (21.4%) and 256/2775 (9.2%) of patients treated with finerenone and placebo, respectively, experienced treatment-emergent â‰¥mild hyperkalemia; 126/2802 (4.5%) and 38/2796 (1.4%) patients, respectively, experienced moderate hyperkalemia. Independent risk factors for â‰¥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

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

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 ≥mild or ≥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 ≥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 ≥mild hyperkalemia; 126/2802 (4.5%) and 38/2796 (1.4%) patients, respectively, experienced moderate hyperkalemia. Independent risk factors for ≥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.

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

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 ≥mild hyperkalemia and >6.0 mmol/L for ≥moderate hyperkalemia, in accordance with latest KDIGO guidance on severity of acute hyperkalemia[9]). 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 of hyperkalemia with finerenone compared with the risk associated with the use of dual RAS inhibition and steroidal MR antagonism.

Methods

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

Patients and Study Design

Patients were included in the trial if they were treated with a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), but not both, with a serum [K^+] ≤4.8 mmol/L at both the run-in and screening visits. CKD was defined as either: (1) persistent, moderately elevated albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30–<300 mg/g), an estimated glomerular filtration rate (eGFR) ≥25–<60 mL/min/1.73 m^2, and a history of diabetic retinopathy; or (2) persistent severely elevated albuminuria (UACR ≥300–≤5000 mg/g) and an eGFR ≥25–<75 mL/min/1.73 m^2. Exclusion criteria included treatment with a steroidal MRA, renin inhibitor, or potassium-sparing diuretic that could not be discontinued ≥4 weeks prior to the screening visit.

Eligible patients were randomized 1:1 to receive oral finerenone or placebo using a computer-generated randomizations schedule and stratified by region (North America, Europe, Asia, Latin America, other), albuminuria at screening (moderately increased, severely increased), and eGFR at screening (25–<45, 45–<60, ≥60 mL/min/1.73 m^2). All patients, investigators, and study personnel (except for the independent data monitoring committee) were masked to treatment allocation.

The study consisted of run-in, screening, and double-blind treatment periods. During the run-in period (4–16 weeks), RAS inhibitor therapy was uptitrated to the maximum tolerated labelled dose, maintained for ≥4 weeks prior to the screening visit. Patients meeting eligibility criteria at the screening visit were subsequently randomized within 2 weeks. Patients received an initial dose of study drug of 10 or 20 mg once daily (od), based on an eGFR at the screening visit of 25–<60 or ≥60 mL/min/1.73 m^2, respectively. After the start of treatment, study drug dose reduction or temporary treatment interruption was allowed at any time for safety reasons.

Serum [K^+] Assessment and Management of Hyperkalemia

At regular study visits (month 1, month 4, and every 4 months thereafter), study drug dosing was based on serum [K^+] and eGFR, assessed at local laboratories (Figure 1). If serum [K^+] was ≤4.8 mmol/L, the dose of study drug was either uptitrated from 10 mg to 20 mg od (provided any eGFR decrease was <30% from the last measured value) or maintained at the 20 mg od dose. If serum [K^+] was >4.8–≤5.5 mmol/L, treatment was continued with the same dose of study drug. When serum [K^+] was >5.5 mmol/L, study drug was temporarily withheld and serum [K^+] rechecked within 72 hours – at this point, if serum [K^+] was ≤5.0 mmol/L, study drug was restarted at the 10 mg od dose; otherwise study drug continued to be withheld until serum [K^+] was ≤5.0 mmol/L. Because this was a double-blind trial, placebo recipients underwent sham up- and downtitration depending on their serum [K^+], and had temporary placebo interruption if serum [K^+] was >5.5 mmol/L, in the same manner as for the finerenone group.

The protocol specified that serum [K^+] should be measured within 4 weeks (±7 days) after a temporary treatment interruption of ≥7 days or after dose adjustments or uptitration of study drug. If the treatment interruption was <7 days, serum [K^+] was measured within 4 months, at the next scheduled study visit. Permanent discontinuation of study drug was recommended if a patient on the 10 mg od dose experienced a recurrent hyperkalemia event soon after a previous event with interruption of study drug (provided the only explanation for the recurring hyperkalemia event was the study drug), or if, in the opinion of the investigator, continuation of treatment was harmful to the patient (Figure 1).

Except for temporary treatment interruption and subsequent dose reductions of study drug in response to elevations in serum [K^+], management of hyperkalemia was at the investigator's discretion based on local guidance. There were no restrictions on the use of potassium supplements or potassium binders during the trial, and a low-potassium diet was not mandated by the protocol. Irrespective of serum [K^+], investigators were instructed to maintain standard-of-care therapy; dose reduction of concomitant RAS inhibitor therapy was not allowed solely to facilitate the maintenance of study drug.

Outcomes

The primary outcome of this *post hoc* safety analysis was ≥mild or ≥moderate hyperkalemia, defined using serum [K^+] thresholds of >5.5 and >6.0 mmol/L, respectively, as assessed quantitatively by the central laboratory at every study visit. Hyperkalemia was also reported as an investigator-reported AE using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms 'hyperkalemia' and 'blood potassium increased', as reported previously.[7] AEs, including elevations in serum [K^+], were considered as treatment emergent if they started or worsened during study drug intake or up to 3 days after any temporary or permanent interruption.

As reported previously, the primary efficacy outcome of the FIDELIO-DKD study was a composite of time to first onset of kidney failure, a sustained ≥40% decrease in eGFR from baseline over ≥4 weeks, or renal death. The key secondary efficacy outcome was a composite of time to first onset of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.[7,10]

Statistical Analyses

Safety analyses were performed in the safety analysis set (all randomized patients without critical Good Clinical Practice [GCP] violations who took ≥1 dose of study drug). Cumulative incidences of hyperkalemia were based on the Aalen–Johansen estimator using death as a competing risk; for the serum [K^+] analyses, patients with elevated baseline values (>5.5 and >6.0 mmol/L, respectively) were censored at day 1. The following baseline variables were used in a multivariate Cox proportional hazards model (model 1) to identify significant independent predictors of ≥mild or ≥moderate hyperkalemia. The variables were selected following a review of the literature and were those deemed biologically plausible by the study investigators. They included the following: age, sex, eGFR categories, serum [K^+] categories, log2 transformed UACR, RAS inhibitor dosing, diuretic use, beta-blocker use, sodium-glucose co-transporter-2 inhibitor (SGLT-2i) use, and study drug assignment. A significance threshold of $P<0.05$ was used to identify significant, independent predictors. Schoenfeld residuals were used to check if the proportional hazards assumption was satisfied for each baseline variable used in the model. Another multivariate Cox proportional hazards model (model 2) was used to describe the interaction of the study drug with each of the baseline variables included in model 1 described above. Model 2 evaluated whether the treatment effect of finerenone on risk of ≥mild or ≥moderate hyperkalemia differed within the subgroups; the likelihood ratio test of the nested models was reported as the *P*-value of the interaction. Restricted cubic splines were used to capture any possible nonlinear effects of the short-term change in serum [K^+] or eGFR (from baseline to month 1 or 4) and the subsequent risk of hyperkalemia. The likelihood ratio test was used for the nested models with and without using the spline function to assess whether the model using splines was a better fit to the data than the standard linear model. The hazard ratio and 95% confidence intervals were plotted for the variable where the spline function had been applied. These values compared a change in the relevant variable with that of a zero change within each treatment group.

Efficacy analyses were performed in the full analysis set, which included all randomized patients excepting 60 patients with critical GCP violations. In time-to-event analyses, the superiority of finerenone versus placebo was tested via a stratified log-rank test; stratification factors were region, eGFR category at screening, and albuminuria category at screening; the statistical assumptions of FIDELIO-DKD have been published previously.[7] All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Data Sharing

Data from this study will be made available in the public domain – the electronic repository and date of data availability will be confirmed by Bayer AG.

Role of the funding source

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

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).

Compared with patients without ≥mild hyperkalemia, patients with treatment-emergent ≥mild hyperkalemia tended to have lower eGFR, higher albuminuria, and higher serum [K^+] at baseline, and were more likely to be treated with a potassium binder but less likely to be treated with a diuretic or an SGLT-2i (Tables 1 and S1). Similar differences were observed between patients with and without treatment-emergent ≥moderate hyperkalemia (Tables S2 and S3).

Multivariate Analysis of Risk Factors for ≥mild and ≥moderate Hyperkalemia

A multivariate Cox proportional hazards regression model identified baseline risk predictors for ≥mild (Figure 3) and ≥moderate (Figure S3) hyperkalemia. Higher baseline serum [K^+] was associated with an increased risk of ≥mild hyperkalemia; the risk was increased 1.5-, 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 baseline, respectively, compared with a serum [K^+] of 4.1–4.5 mmol/L. Likewise, lower eGFR was an independent predictor of hyperkalemia; compared with an eGFR ≥60 mL/min/1.73 m^2, the risk of ≥mild hyperkalemia increased 1.5-fold and 2-fold as eGFR dropped below 45 and 25 mL/min/1.73 m^2, respectively. Patients with an eGFR of 45–<60 mL/min/1.73 m^2 had a similar risk to those with an eGFR ≥60 mL/min/1.73 m^2. Every doubling of UACR was associated with a 1.1-fold increased risk of hyperkalemia. Finally, compared with placebo, assignment to finerenone doubled the risk of hyperkalemia, after adjustment for all other risk factors included in the model. Baseline diuretic or SGLT-2i use and advanced age were associated with lower risk of ≥mild hyperkalemia; baseline RAS inhibitor dosing did not modify hyperkalemia risk.

The magnitude of the increased risk of ≥mild and ≥moderate hyperkalemia with finerenone versus placebo was consistent across subgroups, including sex, baseline CKD severity, and baseline medication use (Figures S4 and S5). Significant treatment interactions were noted for the risk of ≥mild hyperkalemia by baseline serum [K^+] and age (Figure S4).

Short-term Changes in Serum [K^+] and eGFR and the Future Risk of Hyperkalemia

Irrespective of treatment assignment, the risk of ≥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 ≥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 ≥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 ≥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 m^3 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 m^3 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 subgroups. Notably, hyperkalemia was the only AE or serious AE to demonstrate excess cases with finerenone; it was an expected side effect of MR antagonism,[11] and the kidney and CV benefits of finerenone seen in the overall population were maintained in patients at highest risk of hyperkalemia.[7]

These analyses describe the risk factors that independently predicted the development of hyperkalemia in FIDELIO-DKD, including baseline serum [K^+], baseline eGFR, and baseline UACR. Although lower eGFR (<45 mL/min/1.73 m^2) and higher baseline potassium concentration (>4.5 mmol/L) are well-established risk factors for hyperkalemia,[9,12] it is also the case that higher UACR is associated with increased hyperkalemia,[13] although this appears to be less widely recognized; in this analysis, a strong and robust relationship emerged between higher UACR and subsequent occurrence of hyperkalemia. Unlike previous studies that have found male sex and advanced age to be hyperkalemia risk factors,[13-15] we found the converse, and the reasons are unclear. Notably, optimizing RAS inhibition before starting treatment with finerenone did not increase the risk of hyperkalemia, perhaps because RAS inhibitor dosing was individualized during the run-in period (uptitrated to the highest dose that each patient could safely tolerate). The use of diuretics and an SGLT-2i may be prudent strategies to reduce the risk of hyperkalemia. However, because few patients were treated with an SGLT-2i at baseline (partly because SGLT-2i use at the time of the study was restricted to patients with higher eGFR values) these results should be interpreted with caution.

Short-term increases in serum [K^+] after the start of treatment were predictive of subsequent risk of hyperkalemia; this risk was shared between placebo and finerenone. However, for any given increase in serum [K^+] between baseline and month 4 versus no change, the increased risk of hyperkalemia was smaller with finerenone than placebo. These findings may appear counterintuitive but can be explained by the following considerations: finerenone is expected to increase serum [K^+] through MR antagonism, which may have triggered changes in management, such as finerenone treatment interruption and dose reduction, or adding other therapies (such as diuretics or potassium binders) that might mitigate the subsequent risk of hyperkalemia.[9] On the other hand, increases in serum [K^+] provoked by placebo may reflect processes in the kidney that reduce its ability to secrete potassium, such as acute kidney injury, tubulointerstitial inflammation, or obstruction[16]; these are less amenable to treatment interventions (evidence on the effectiveness of potassium binders and loop diuretics in an acute setting are lacking) and are unaffected by reducing the dose of placebo.[9]

Short-term decreases in eGFR after the start of treatment were associated with an increased risk of hyperkalemia during the study, and the magnitude of the increased risk for any given reduction in eGFR versus no change in eGFR was smaller with finerenone than with placebo. Provoked by natriuresis or modest blood pressure reduction, the decrease in eGFR induced by finerenone is hemodynamic (in contrast to a tubular cause) and is less likely to impair the ability to secrete potassium. Therefore, temporary treatment interruption and finerenone dose reduction are likely to restore eGFR towards normal and normalize serum [K^+]. On the other hand, short-term decreases in eGFR in patients receiving placebo may be due to tubular factors or obstructive uropathy, which also impair the ability to secrete potassium,[9] thus increasing the subsequent risk of hyperkalemia. Moreover, because finerenone slows eGFR decline versus placebo, this may reduce the risk of subsequent hyperkalemia.[7]

Relative to the incidence of hyperkalemia in FIDELIO-DKD, a higher incidence was reported in trials using dual RAS inhibition.[4-6] In VA NEPHRON-D, 32/724 (4.4%) patients in the losartan group, and 72/724 (9.9%) patients in the losartan plus lisinopril group experienced severe hyperkalemia (defined as serum [K^+] >6.0 mmol/L, or hyperkalemia requiring a visit to the emergency room, hospitalization, or dialysis). Thus, in the VA NEPHRON-D study, 18 patients would have needed to have been prescribed dual RAS blockade for 1 patient to develop severe hyperkalemia.[5] Similarly, looking at hyperkalemia events leading to permanent treatment discontinuation in ALTITUDE and ORIENT, a small number of patients (45 and 26 patients, respectively) would have needed to be treated with dual RAS blockade before 1 patient would have needed to stop treatment because of hyperkalemia.[4,6] In contrast, in FIDELIO-DKD, 71 patients would have needed to be prescribed finerenone before 1 patient permanently stopped the drug.[7] Furthermore, in FIDELIO-DKD, finerenone significantly reduced the risk of the composite kidney and CV outcomes (by 18% and 14%, respectively) compared with placebo, whereas the dual RAS-inhibitor studies failed to demonstrate kidney or CV benefits.[4-6]

A common comparator for a nonsteroidal MRA, albeit not indicated for patients with CKD, is the steroidal MRA spironolactone. A *Cochrane Database Systematic* review of 27 small studies including patients with CKD stages 1–4 with and without diabetes (*N*=1549) noted that spironolactone plus an ACEi or ARB decreased albuminuria and blood pressure, doubled the risk of hyperkalemia, and increased the risk of gynecomastia 5-fold, with insufficient data to analyze benefits on clinical outcomes such as end-stage kidney disease.[17] The active metabolites of spironolactone have a long half-life.[11,18] In the AMBER study, which included patients with CKD (eGFR 25–45 mL/min/1.73 m^2) and resistant hypertension, an exploratory analysis showed that 75% of patients still had detectable urinary metabolites of spironolactone 2 weeks after stopping treatment. Moreover, approximately 2 in 3 patients developed ≥mild hyperkalemia and approximately 1 in 4 patients had to discontinue spironolactone because of hyperkalemia within 12 weeks. Even when given the potassium-binding drug patiromer, over 30% of patients developed ≥mild hyperkalemia and 6.8% of patients stopped spironolactone because of hyperkalemia.[19] These high rates of hyperkalemia and discontinuation of spironolactone in AMBER suggest that the incidence of hyperkalemia with finerenone may be lower than with spironolactone in comparable patient populations. In addition, in a head-to-head phase 2 study in patients with heart failure with reduced ejection fraction and CKD, the incidence of hyperkalemia was 11.1% with spironolactone (25–50 mg od) compared with 4.8% with finerenone (10 mg od).[20] Once-daily oral administrations of 5 mg and 10 mg of finerenone were at least as effective as spironolactone (25 mg or 50 mg/day) in decreasing cardiorenal biomarker levels, but resulted in smaller increases in serum potassium, lower incidences of hyperkalemia and worsening renal function, and smaller reductions in systolic blood pressure.[20] These observations suggest that some pharmacodynamic effects mediated by MRAs, including blood pressure control or serum potassium changes, are the consequence of a significant drug exposure over a long period (long half-life, area-under-the-curve driven), whereas others (e.g. anti-inflammatory, anti-hypertrophic, and anti-fibrotic effects) are the consequences of relatively short drug exposure (short half-life, C_{max} driven) triggered by different signaling cascades. Strikingly, the rise in serum potassium with finerenone 5 mg twice daily was larger in comparison with finerenone 10 mg od, whereas reductions of N-terminal pro–B-type natriuretic peptide or albuminuria were similar.[20] This differential effect of once- versus twice-daily dosing of finerenone illustrates the importance of consideration of both pharmacokinetics and physiology when considering hyperkalemia rates. It is likely that the low absolute risk of hyperkalemia with finerenone is because of its unique attributes: the short half-life of the drug, absence of active metabolites, balanced kidney–heart distribution (in rodent models) and the novel mechanism of action involving distinct blockade of the MR and different effects on subsequent gene expression.[11] Notably, because of the short half-life of finerenone (2–3 hours in patients with CKD) and lack of active metabolites,[11,21] finerenone-associated hyperkalemia can be effectively managed by treatment interruption, as demonstrated in FIDELIO-DKD. It is important to highlight that these properties contrast with the long half-life and multiple active metabolites of spironolactone, as well as the fact that spironolactone has a kidney versus heart tissue distribution of approximately 6:1 (~1:1 for finerenone) in rodent models, and that spironolactone interacts with the MR in a different manner to finerenone.[11,21]

Esaxerenone is a potent and highly selective nonsteroidal MRA with a much longer half-life (~19 hours) than finerenone.[22] In a patient population with less advanced CKD and T2D, 52 weeks of treatment with esaxerenone led to discontinuation due to elevated serum [K^+] in 4.0% of patients compared with 0.4% of patients receiving placebo.[23,24] Another steroidal MRA, eplerenone, which is more selective than spironolactone, approximately doubles the risk of hyperkalemia in patients with heart failure,[25,26] and is contraindicated in patients with T2D and moderately elevated albuminuria without heart failure (in the USA).[27]

Results from the FIDELIO-DKD trial provide insights into requirements for serum [K^+] monitoring in patients treated with finerenone. The earliest time point after which serum [K^+] was measured was 1 month after treatment initiation. Very few patients developed hyperkalemia at this time: 86/2742 (3.1%) and 34/2730 (1.2%) patients in the finerenone and placebo groups, respectively. The second scheduled serum [K^+] assessment was at month 4 following treatment initiation, and at four monthly intervals thereafter. The frequency of potassium monitoring employed in FIDELIO-DKD was similar to the frequency of monitoring recommended for patients with CKD in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (3–4 times a year for patients with UACR >300 mg/g and eGFR <60 mL/min/1.73 m^2, and 2–3 times a year for patients with UACR 30–300 mg/g and eGFR 15–59 mL/min/1.73 m^2).[3] Evidence from routine clinical practice suggests that physicians often intervene and reduce the dose of RAS inhibitors when serum [K^+] rises above 5.0 mmol/L[28]; in FIDELIO-DKD, RAS inhibitor dose reduction was not permitted and finerenone was continued with no dose adjustments in patients with a serum [K^+] between 5.0–5.5 mmol/L. It was only when serum [K^+] rose to >5.5 mmol/L that finerenone was temporarily withheld. Treatment was resumed (at the 10 mg dose) when serum [K^+] was ≤5.0 mmol/L. The occurrence of serum [K^+] >5.5 or >6.0 mmol/L accumulated gradually over time and could occur months or years after starting finerenone. This may be related to two important determinants of hyperkalemia: declining kidney function and increasing serum [K^+], or a combination of both.[29] Thus, potassium monitoring at each clinical follow-up visit would be a prudent strategy, in addition to both physicians and patients being aware of conditions or triggers that may precipitate a hyperkalemia event, such as medications (e.g.

trimethoprim), acute illness, volume depletion, and acute kidney injury.[29,30] The FIDELIO-DKD protocol has established a reliable potassium management algorithm, aligned to current guidelines,[3] that may serve as a framework for use in clinical practice, taking into consideration patient characteristics (i.e. eGFR and baseline serum [K^+]) that may increase their risk of hyperkalemia.

In summary, these analyses from FIDELIO-DKD characterize the risk of hyperkalemia in patients with CKD and T2D, reporting that finerenone was associated with a low absolute risk of clinically relevant hyperkalemia, with only a small proportion of events having a clinical impact. These analyses contribute to the understanding of how clinical characteristics, established risk factors, and treatment with finerenone may interact. Notably, elevated serum [K^+] and lower eGFR when starting treatment with finerenone did not abrogate kidney or CV benefits of finerenone. These data provide a robust basis for incorporation of finerenone into clinical practice, with routine potassium monitoring for patients with CKD and T2D considered appropriate to manage the risk of hyperkalemia.

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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PK is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. He is the co-inventor of finerenone and holds US and European patents relating to finerenone (US8436180B2 and EP2132206B1) and patents and inventions with Bayer AG.

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DW is a full-time employee of Bayer AG, Cardiorenal Medical Affairs, United States; and Other Interests/Relationships: Senior Director - Nephrology; US Medical Affairs.

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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.
[a]Information 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)

[a]In 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.

[b]Actions 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. [a]if estimated glomerular filtration rate is stable (i.e. ≤30% decrease since last available measurement); [b]uptitration visits were performed at 4 weeks ±7 days after any treatment interruption >7 days and after any uptitration; [c]Regular study visits were scheduled at month 1, month 4, and every 4 months thereafter; [d]if treatment interruption ≤7 days.

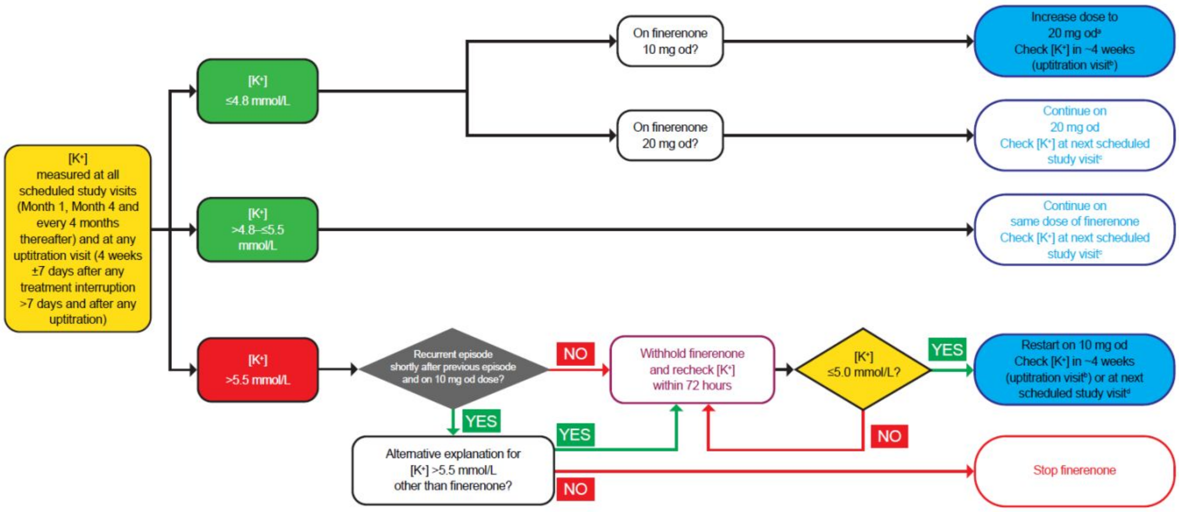


Figure 1. Potassium management algorithm in FIDELIO-DKD

Figure 2. Time to treatment-emergent serum potassium concentration (A) >5.5 mmol/L and (B) >6.0 mmol/L.
[a]Cumulative incidence calculated by Aalen–Johansen estimator using all-cause death as a competing risk; [b]incidence calculated as *n*/*N* over 2.6 years' median follow-up; [c]patients at risk must have both a baseline and post-baseline treatment-emergent value and the baseline value must be below the threshold.

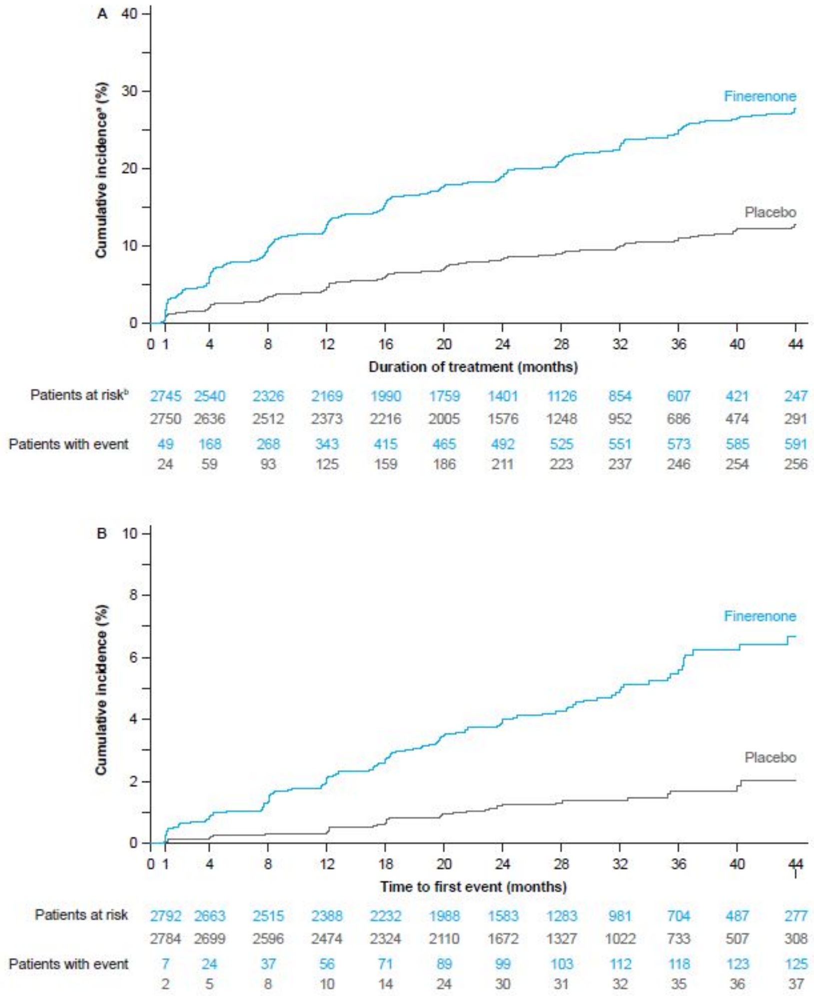
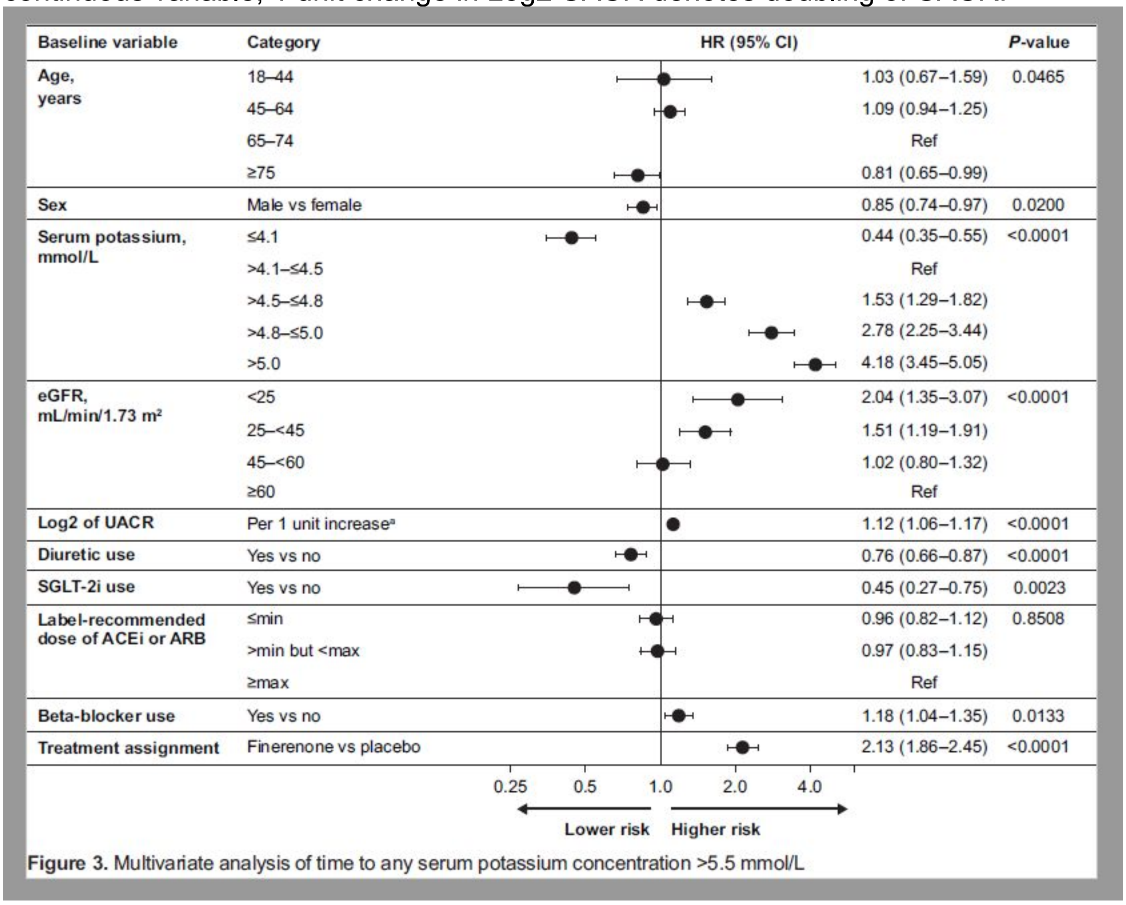


Figure 2. Time to treatment-emergent serum potassium concentration >5.5 mmol/L

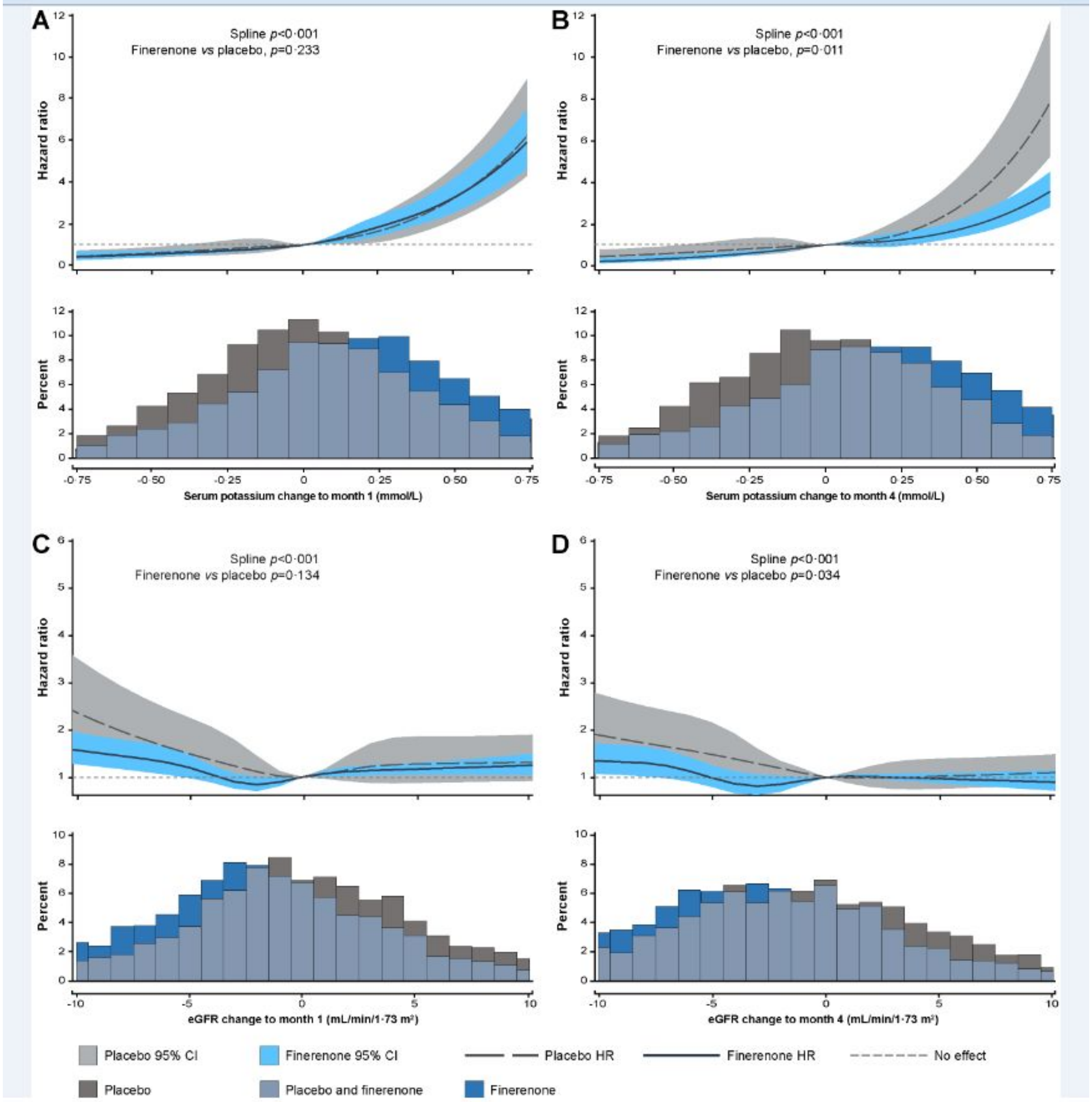
Figure 3. Multivariate analysis of time to any serum potassium concentration >5.5 mmol/L. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine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



Baseline variable	Category	HR (95% CI)	*P*-value
Age, years	18–44	1.03 (0.67–1.59)	0.0465
	45–64	1.09 (0.94–1.25)	
	65–74	Ref	
	≥75	0.81 (0.65–0.99)	
Sex	Male vs female	0.85 (0.74–0.97)	0.0200
Serum potassium, mmol/L	≤4.1	0.44 (0.35–0.55)	<0.0001
	>4.1–≤4.5	Ref	
	>4.5–≤4.8	1.53 (1.29–1.82)	
	>4.8–≤5.0	2.78 (2.25–3.44)	
	>5.0	4.18 (3.45–5.05)	
eGFR, mL/min/1.73 m²	<25	2.04 (1.35–3.07)	<0.0001
	25–<45	1.51 (1.19–1.91)	
	45–<60	1.02 (0.80–1.32)	
	≥60	Ref	
Log2 of UACR	Per 1 unit increase[a]	1.12 (1.06–1.17)	<0.0001
Diuretic use	Yes vs no	0.76 (0.66–0.87)	<0.0001
SGLT-2i use	Yes vs no	0.45 (0.27–0.75)	0.0023
Label-recommended dose of ACEi or ARB	≤min	0.96 (0.82–1.12)	0.8508
	>min but <max	0.97 (0.83–1.15)	
	≥max	Ref	
Beta-blocker use	Yes vs no	1.18 (1.04–1.35)	0.0133
Treatment assignment	Finerenone vs placebo	2.13 (1.86–2.45)	<0.0001

Figure 3. Multivariate analysis of time to any serum potassium concentration >5.5 mmol/L

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

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, *n* (%)				
<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, *n* (%)				
<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, *n* (%)				
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, *n* (%)	986 (45.8)	1111 (45.3)	315 (46.6)	188 (49.7)

Label-recommended dose of RASi, *n* (%)[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, *n* (%)	1101 (51.2)	1304 (53.2)	359 (53.1)	201 (53.2)
Diuretic, *n* (%)				
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, *n* (%)	43 (2.0)	48 (2.0)	27 (4.0)	18 (4.8)
Potassium supplements, *n* (%)	74 (3.4)	82 (3.3)	11 (1.6)	3 (0.8)
Glucose-lowering therapies, *n* (%)	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.

[a]Information 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, *n* (%)		
No	4443 (81.8)	153 (67.1)
Yes	987 (18.2)	75 (32.9)
Label-recommended dose of RASi, *n* (%)[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, *n* (%)	2855 (52.6)	110 (48.2)
Diuretic, *n* (%)	3102 (57.1)	102 (44.7)
Loop	1560 (28.7)	53 (23.2)
Thiazide	1310 (24.1)	41 (18.0)
Potassium binders, *n* (%)	123 (2.3)	13 (5.7)
Potassium supplements, *n* (%)	164 (3.0)	6 (2.6)
Glucose-lowering therapies, *n* (%)	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.

[a]Information 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

eGFR category, mL/min/1.73 m^2, *n* (%)				
<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, *n* (%)				
<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, *n* (%)				
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, *n* (%)	1237 (46.2)	1257 (45.7)	64 (43.5)	42 (51.9)
Label-recommended dose of RASi, *n* (%)[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, *n* (%)	1389 (51.8)	1466 (53.3)	71 (48.3)	39 (48.1)
Diuretic, *n* (%)	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, *n* (%)	63 (2.4)	60 (2.2)	7 (4.8)	6 (7.4)
Potassium supplements, *n* (%)	81 (3.0)	83 (3.0)	4 (2.7)	2 (2.5)
Glucose-lowering therapies, *n* (%)	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.

[a]Information 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, *n* (%)	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, *n* (%)	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

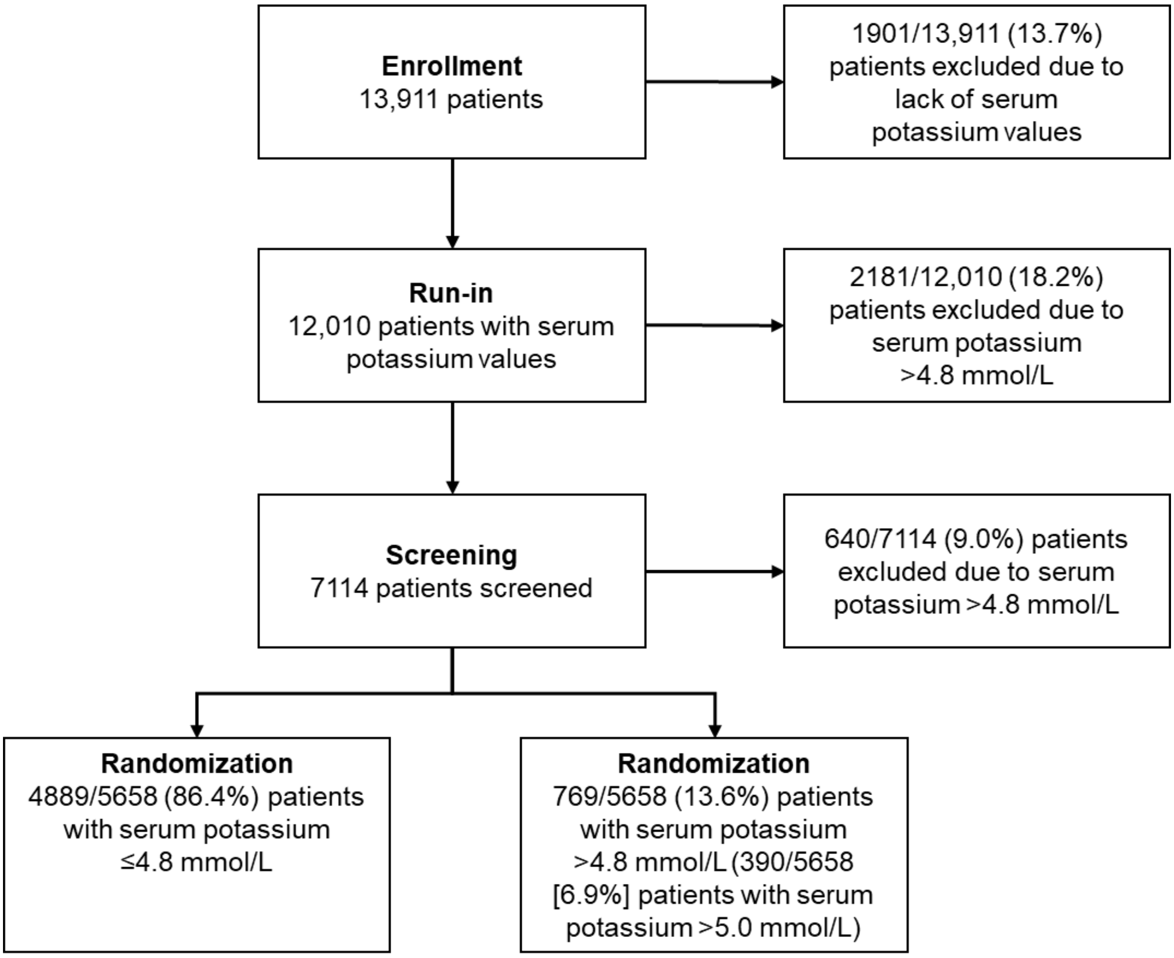

Figure S1. Flow of patients through the study from enrollment to randomization based on inclusion/exclusion related to serum potassium measurements.

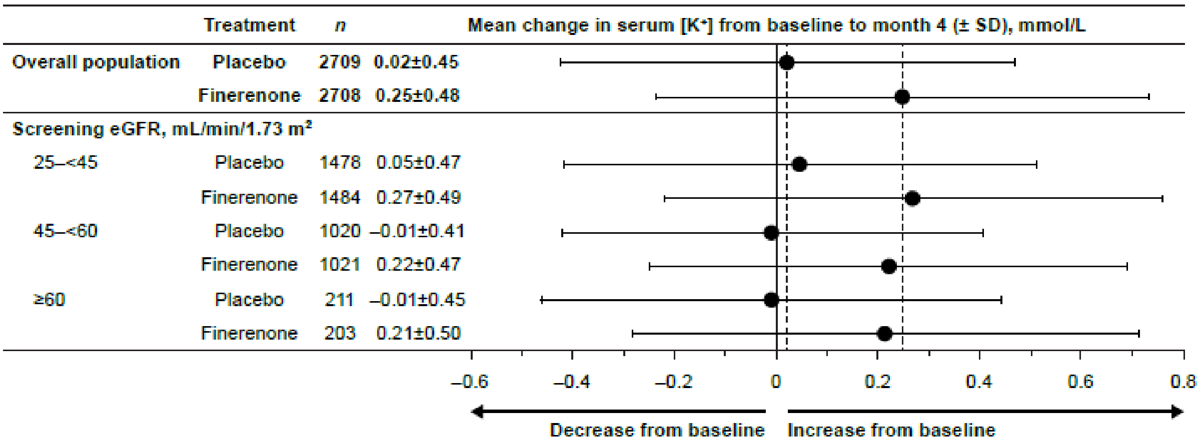

Figure S2. Mean change in serum potassium concentration from baseline to month 4 in the overall population and by eGFR category at the screening visit. eGFR, estimated glomerular filtration rate; SD, standard deviation.

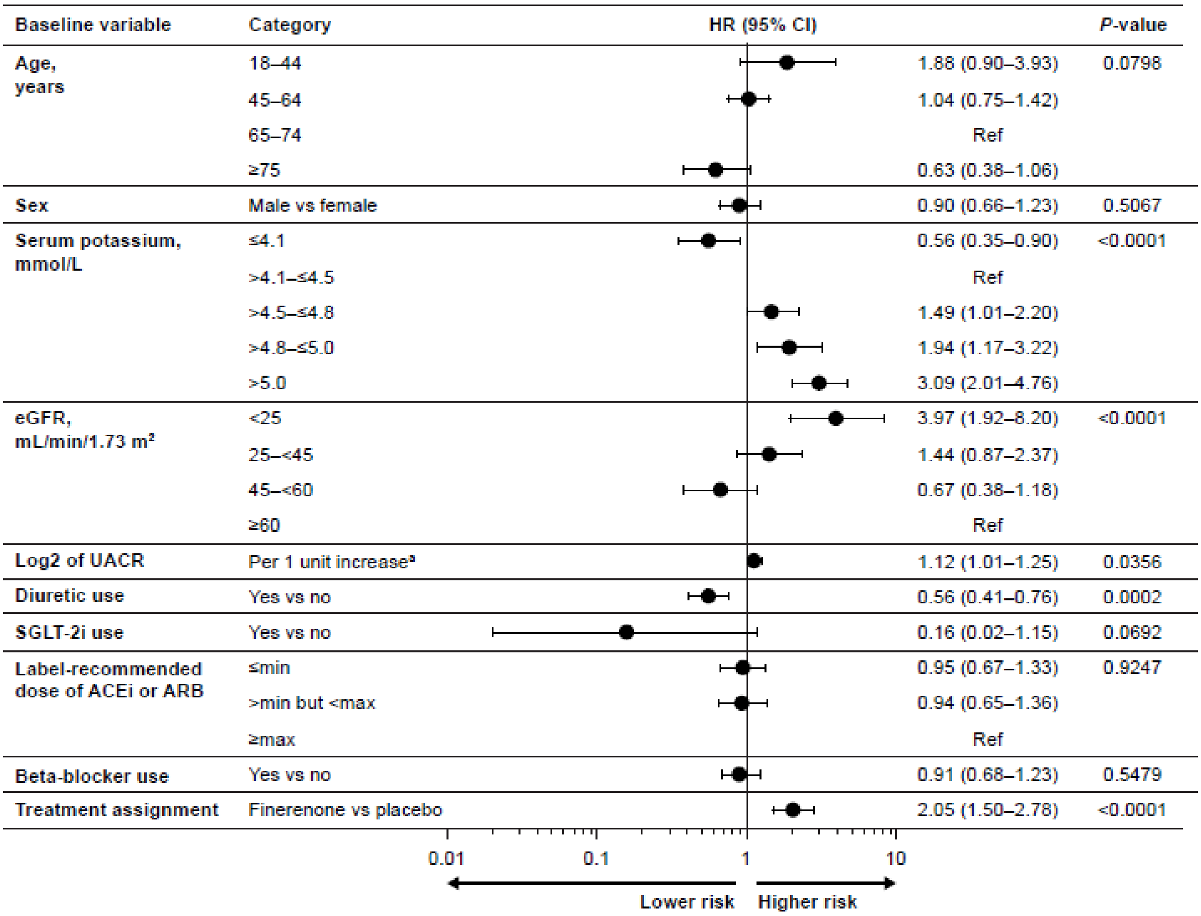

Figure S3. Multivariate analysis of time to any serum potassium concentration >6.0 mmol/L. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio. [a]UACR is modelled as a continuous variable; 1 unit change in Log2 UACR denotes doubling of UACR.

Baseline variable	Category	Finerenone *n*/100 PYs	Placebo *n*/100 PYs	HR (95% CI)	$P_{interaction}$
Overall		10.0	4.8	2.12 (1.85–2.43)	
Sex	Male	9.3	4.4	2.15 (1.82–2.54)	0.8176
	Female	11.8	5.6	2.08 (1.64–2.63)	
Age, years	18–44	10.7	7.0	1.04 (0.45–2.41)	0.0064
	45–64	10.4	5.9	1.71 (1.40–2.10)	
	65–74	10.3	4.0	2.74 (2.20–3.41)	
	≥75	8.3	3.7	2.26 (1.54–3.32)	
Serum potassium, mmol/L	≤4.1	3.6	1.7	2.18 (1.45–3.26)	0.0152
	>4.1–≤4.5	8.5	3.7	2.33 (1.81–3.00)	
	>4.5–≤4.8	14.3	5.4	2.55 (1.94–3.35)	
	>4.8–≤5.0	24.3	10.2	2.39 (1.64–3.48)	
	>5.0	32.1	22.5	1.31 (0.97–1.78)	
eGFR, mL/min/1.73 m²	<25	15.9	11.2	1.30 (0.65–2.58)	0.1756
	25–<45	12.5	5.4	2.25 (1.89–2.68)	
	45–<60	7.7	3.6	2.25 (1.72–2.94)	
	≥60	6.0	4.0	1.49 (0.96–2.33)	
	<30	10.8	7.3	4.23 (0.70–25.5)	0.7119
UACR, mg/g	30–<300	10.5	4.2	2.24 (1.53–3.28)	
	≥300	9.9	4.8	2.10 (1.81–2.43)	
Diuretic use	No	11.6	5.7	2.03 (1.67–2.46)	0.5033
	Yes	8.8	4.1	2.22 (1.83–2.70)	
SGLT-2 inhibitor use	No	10.3	4.9	2.11 (1.83–2.42)	0.3684
	Yes	3.7	1.2	3.57 (1.14–11.2)	
Label-recommended dose of ACEi or ARB	≤min	10.3	4.8	2.22 (1.74–2.84)	0.8415
	>min but <max	10.7	5.0	1.99 (1.53–2.60)	
	≥max	9.5	4.6	2.13 (1.73–2.63)	
Beta-blocker use	No	9.5	4.8	1.99 (1.63–2.43)	0.3869
	Yes	10.5	4.7	2.24 (1.86–2.71)	

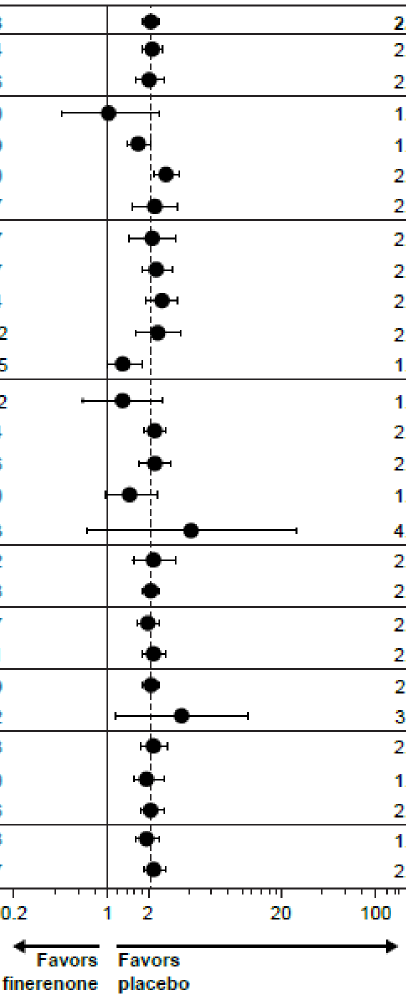

Figure S4. Impact of finerenone on hyperkalemia risk (serum potassium concentration >5.5 mmol/L) in patient subgroups. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-year;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

Baseline variable	Category	Finerenone	Placebo	HR (95% CI)	$P_{interaction}$
		n/100 PYs			
Overall		**1.8**	**0.9**	**2.06 (1.51–2.80)**	
Sex	Male	1.6	0.9	1.94 (1.34–2.83)	0.6094
	Female	2.2	0.9	2.31 (1.34–3.99)	
Age, years	18–44	4.4	1.8	1.74 (0.41–7.34)	0.0945
	45–64	1.8	1.1	1.48 (0.94–2.32)	
	65–74	1.8	0.9	2.19 (1.37–3.52)	
	≥75	1.7	0.1	18.2 (2.43–137)	
Serum potassium, mmol/L	≤4.1	0.7	0.5	1.54 (0.69–3.42)	0.2380
	>4.1–≤4.5	1.7	0.6	3.05 (1.66–5.59)	
	>4.5–≤4.8	2.2	1.3	1.65 (0.92–2.94)	
	>4.8–≤5.0	3.6	0.9	4.16 (1.39–12.40)	
	>5.0	4.5	3.1	1.39 (0.70–2.76)	
eGFR, ml/min/1.73 m²	<25	6.8	2.7	2.95 (0.90–9.67)	0.2452
	25–<45	2.3	1.0	2.36 (1.59–3.51)	
	45–<60	1.0	0.5	1.89 (0.94–3.79)	
	≥60	1.0	1.1	0.87 (0.34–2.20)	
	<30	3.4	3.4	3.39 (0.21–55.7)	0.8853
UACR, mg/g	30–<300	1.5	0.7	1.76 (0.72–4.33)	
	≥300	1.8	0.9	2.09 (1.50–2.90)	
Diuretic use	No	2.5	1.1	2.23 (1.48–3.37)	0.5504
	Yes	1.3	0.7	1.85 (1.16–2.94)	
SGLT-2 inhibitor use	No	1.9	0.9	2.04 (1.50–2.78)	NA
	Yes	0.3	0	NA	
Label-recommended dose of ACEi or ARB	≤min	2.0	0.9	2.21 (1.28–3.81)	0.9379
	>min but <max	1.8	0.8	2.08 (1.11–3.88)	
	≥max	1.7	0.9	1.94 (1.22–3.09)	
Beta-blocker use	No	2.0	1.0	1.93 (1.27–2.94)	0.6616
	Yes	1.6	0.8	2.21 (1.41–3.48)	

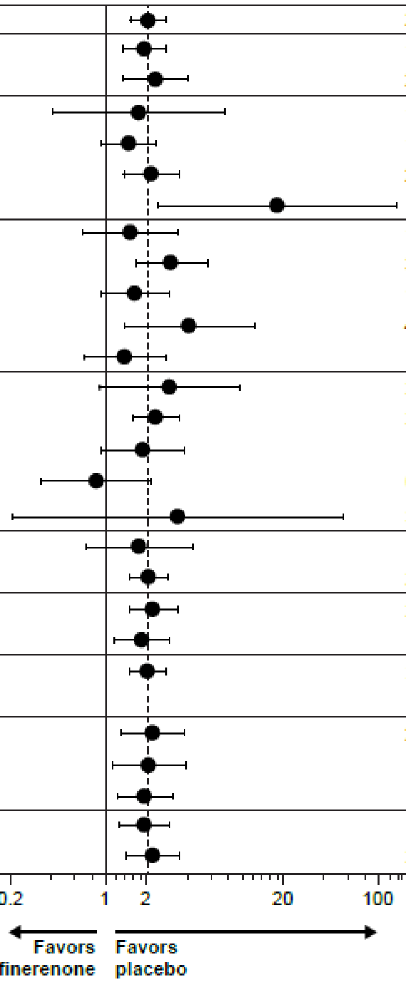

Figure S5. Impact of finerenone on hyperkalemia (serum potassium concentration >6.0 mmol/L) in patient subgroups. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-year;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

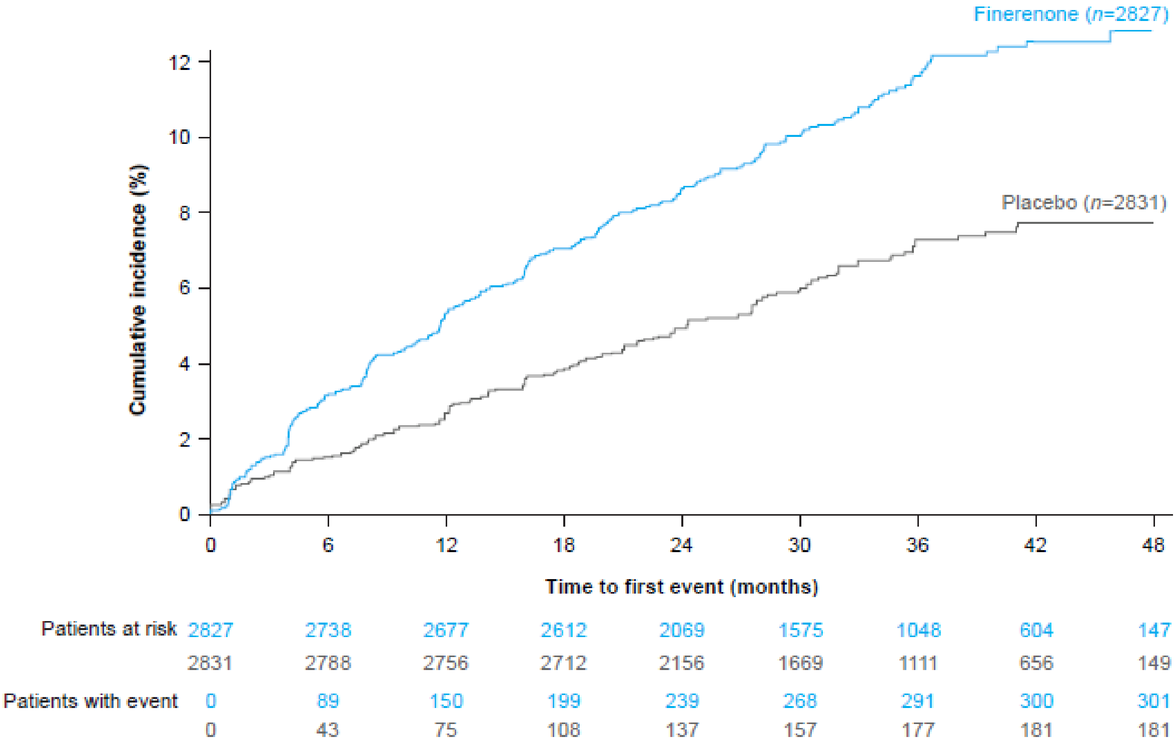

Figure S6. Time to first use of potassium binders.

Outcome and subgroup	Finerenone (Patients with an event, n/N)	Placebo (Patients with an event, n/N)	Finerenone (Patients with an event, n/100 PYs)	Placebo (Patients with an event, n/100 PYs)	HR (95% CI)	$P_{interaction}$
Primary kidney-specific endpoint[a]						
All patients	**504/2833**	**600/2841**	**7.59**	**9.08**	**0.82 (0.73–0.93)**	
Baseline eGFR, mL/min/1.73 m²						0.85
<25	18/66	23/69	13.35	16.53	0.88 (0.48–1.64)	
25–<45	295/1476	339/1505	8.66	9.81	0.86 (0.73–1.00)	
45–<60	138/972	168/928	5.95	7.69	0.77 (0.61–0.96)	
≥60	53/318	70/338	6.77	8.47	0.78 (0.55–1.12)	
Baseline serum [K⁺], mmol/L						0.87
<4.8	407/2302	487/2295	7.52	9.08	0.82 (0.72–0.94)	
≥4.8–5.0	61/333	76/349	7.76	9.52	0.80 (0.57–1.12)	
>5.0	36/197	37/196	8.08	8.34	0.93 (0.58–1.47)	
Baseline eGFR 25–<45 mL/min/1.73 m² and baseline serum [K⁺] >4.5 mmol/L						0.71
No	406/2297	487/2307	7.48	9.03	0.81 (0.71–0.93)	
Yes	98/535	113/533	8.05	9.31	0.86 (0.66–1.13)	
Key secondary CV endpoint[b]						
All patients	**367/2833**	**420/2841**	**5.11**	**5.92**	**0.86 (0.75–0.99)**	
Baseline eGFR, mL/min/1.73 m²						0.18
<25	8/66	19/69	4.97	12.12	0.40 (0.18–0.92)	
25–<45	212/1476	224/1505	5.78	6.00	0.95 (0.78–1.14)	
45–<60	106/972	126/928	4.22	5.46	0.78 (0.60–1.01)	
≥60	40/318	51/338	4.74	5.70	0.85 (0.56–1.28)	
Baseline serum [K⁺], mmol/L						0.84
<4.8	297/2302	335/2295	5.07	5.81	0.87 (0.75–1.02)	
≥4.8–5.0	46/333	57/349	5.47	6.68	0.81 (0.55–1.20)	
>5.0	23/197	28/196	4.70	5.96	0.76 (0.43–1.31)	
Baseline eGFR 25–<45 mL/min/1.73 m² and baseline serum [K⁺] >4.5 mmol/L						0.49
No	296/2297	348/2307	5.03	6.02	0.84 (0.72–0.98)	
Yes	70/535	72/533	5.37	5.49	0.95 (0.68–1.32)	
All-cause mortality						
All patients	**219/2833**	**244/2841**	**2.90**	**3.23**	**0.90 (0.75–1.07)**	
Baseline eGFR, mL/min/1.73 m²						0.22
<25	7/66	14/69	4.14	8.30	0.49 (0.20–1.21)	
25–<45	133/1476	130/1505	3.43	3.27	1.04 (0.82–1.32)	
45–<60	56/972	72/928	2.14	2.94	0.74 (0.52–1.05)	
≥60	22/318	28/338	2.46	2.95	0.82 (0.47–1.43)	
Baseline serum [K⁺], mmol/L						0.35
<4.8	173/2302	183/2295	2.80	2.98	0.95 (0.77–1.16)	
≥4.8–5.0	26/333	32/349	2.97	3.53	0.84 (0.50–1.41)	
>5.0	19/197	29/196	3.71	5.90	0.60 (0.34–1.08)	
Baseline eGFR 25–<45 mL/min/1.73 m² and baseline serum [K⁺] >4.5 mmol/L						0.79
No	170/2297	193/2307	2.74	3.12	0.88 (0.72–1.08)	
Yes	48/535	51/533	3.51	3.73	0.93 (0.63–1.39)	

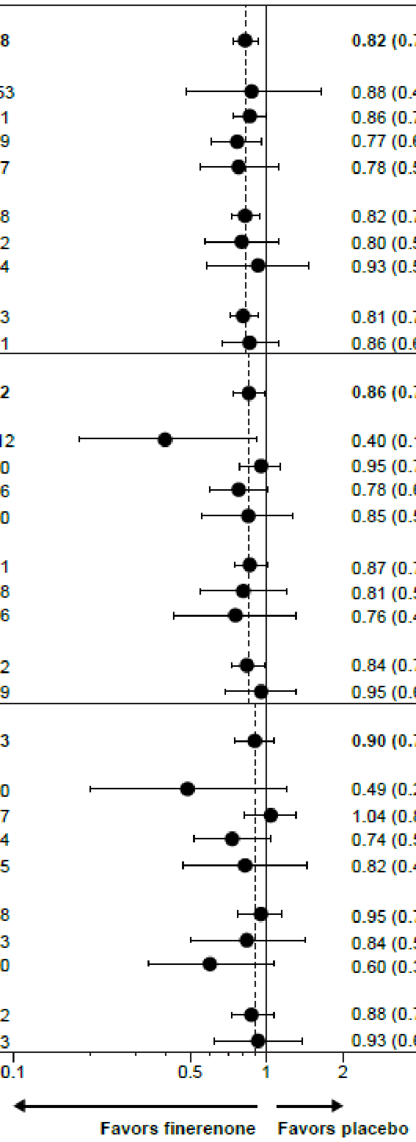

Figure S7. Primary composite kidney, key secondary composite CV, and all-cause mortality outcomes in patient subgroups at highest risk of hyperkalemia. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; [K⁺], potassium concentration; MI, myocardial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

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