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► **To cite this version:**

Finnian Mc Causland, Muthiah Vaduganathan, Brian Claggett, Ian Kulac, Akshay Desai, et al.. Finerenone and Kidney Outcomes in Patients with Heart Failure: The FINEARTS-HF Trial. *Journal of the American College of Cardiology*, 2024, 10.1016/j.jacc.2024.10.091 . hal-04791163

HAL Id: hal-04791163

<https://hal.univ-lorraine.fr/hal-04791163v1>

Submitted on 19 Nov 2024

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Journal Pre-proof



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PII: S0735-1097(24)10252-5

DOI: <https://doi.org/10.1016/j.jacc.2024.10.091>

Reference: JAC 31516

To appear in: *Journal of the American College of Cardiology*

Received Date: 5 October 2024

Revised Date: 21 October 2024

Accepted Date: 21 October 2024

Please cite this article as: Mc Causland FR, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, Henderson AD, Brinker M, Perkins R, Scheerer MF, Schloemer P, Lam CSP, Senni M, Shah SJ, Voors AA, Zannad F, Pitt B, McMurray JJV, Solomon SD, Finerenone and Kidney Outcomes in Patients with Heart Failure: The FINEARTS-HF Trial, *Journal of the American College of Cardiology* (2024), doi: <https://doi.org/10.1016/j.jacc.2024.10.091>.

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Finerenone and Kidney Outcomes in Patients with Heart Failure: The FINEARTS-HF Trial

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Running Title: Finerenone and kidney outcomes in HFmrEF and HFpEF

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FUNDING

FINEARTS-HF was sponsored by Bayer.

Role of Funder/Sponsor

FINEARTS-HF was designed by the academic members of the executive committee in collaboration with representatives from Bayer. The sponsor, Bayer, was responsible for study supervision, site monitoring, and data collection. Primary data analysis was performed by Bayer and independent academic statisticians at the Brigham and Women's Hospital, Boston. The present analyses were conducted by an independent academic group at Brigham and Women's Hospital. All authors participated in the decision to submit the manuscript for publication with support from the study sponsor.

Disclosures

Dr. Mc Causland reports research funding from NIDDK, Satellite Healthcare, Fifth Eye, Novartis, and Lexicon paid directly to his institution; consulting fees from GSK and Zydus Therapeutics; expert witness fees from Rubin-Anders Scientific.

Dr. Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics.

Dr Claggett has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, Rocket, and has served on a data safety monitoring board for Novo Nordisk.

Dr. Kulac reports no relationships relevant to the contents of this paper.

Dr. Desai has received institutional research grants (to Brigham and Women's Hospital) from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer as well as personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, Veristat, Verily, Zydus.

Dr. Jhund reports speakers' fees from AstraZeneca, Novartis, Alkem Laboratories, ProAdWise Communications, Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics. PSJ's employer the University of Glasgow has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis and Novo Nordisk. Director GCTP Ltd.

Dr. Henderson reports no financial conflicts of interest.

Drs. Brinker, Perkins, Scheerer, and Schloemer are full-time employees of Bayer.

Dr. Lam has received research support from NovoNordisk and Roche Diagnostics; has received consulting fees from Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and is a co-founder & non-executive director of Us2.ai.

Dr. Senni has served on Advisory Boards, Consultancy and Honoraria for Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novonordisk, Bayer, Boehringer Ingelheim.

Dr. Shah has received research grants from NIH (U54 HL160273, X01 HL169712, R01 HL140731, R01 HL149423), AHA (24SFRNPCN1291224), AstraZeneca, Corvia, and Pfizer and consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics.

Dr. Voor's employer received consultancy fees and/or research support from Adrenomed, Anacardio, AstraZeneca, Bayer AG, BMS, Boehringer Ingelheim, Corteria, EliLilly, Merck, Moderna, Novartis, Novo Nordisk, Roche diagnostics, SalubrisBio.

Dr. Zannad reports personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, BMS, CVRx, Cambrian, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, NovoNordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, USa2, having stock options at G3Pharmaceutical and equities at Cereno, Cardiorenal, Eshmoun Clinical research and being the founder of Cardiovascular Clinical Trialists.

Dr. Pitt has served as a consultant for Bayer, Astra Zeneca, Bristol Meyers Squibb, Boehringer Ingelheim, Lexicon, Anacardia, and G3 Pharmaceuticals. He has served as a consultant and received stock options or stocks from Sea Star Medical, Vifor, scPharmaceuticals, SQinnovations, KBP Biosciences, Sarfez, Cereno Scientific, Prointel, and Brainstorm Medical. He holds a US Patent (9931412-site specific delivery of Eplerenone to the myocardium) and has a US Patent pending (63/045,783 HistoneModulating agents for the prevention and treatment of organ damage).

Dr. McMurray reports payments through Glasgow University from work on clinical trials, consulting and grants from: Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK and Novartis. Personal consultancy fees from: Alynlyam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, BMS, Cardurion, Cytokinetics, Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, River 2 Renal Corp., British Heart Foundation, National Institute for Health – National Heart Lung and Blood Institute (NIH-NHLBI), Boehringer Ingelheim, SQ Innovations, Catalyze Group. Personal lecture fees: Abbott, Alkem Metabolics, Astra Zeneca, Blue Ocean Scientific Solutions Ltd., Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd., Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharmaceuticals Ltd., Lupin Pharmaceuticals, Medscape/Heart.Org., ProAdWise Communications, Radcliffe Cardiology,

Sun Pharmaceuticals, The Corpus, Translation Research Group, Translational Medicine Academy.
Data Safety Monitoring Board: WIRB-Copernicus Group Clinical Inc. He is a director of Global
Clinical Trial Partners Ltd.

Dr. Solomon has received research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Valo

Abstract

Background: Finerenone has kidney protective effects in patients with chronic kidney disease (CKD) with type 2 diabetes, but effects on kidney outcomes in patients with heart failure (HF) with and without diabetes and/or CKD are not known.

Objectives: Examine the effects of finerenone on kidney outcomes in FINEARTS-HF, a randomized trial of finerenone vs. placebo among patients with HF with mildly reduced or preserved ejection fraction.

Methods: We explored the effects of finerenone on the secondary outcome of a sustained $\geq 50\%$ eGFR decline or kidney failure (sustained eGFR decline < 15 mL/min/1.73 m²; initiation of maintenance dialysis; renal transplant). In this prespecified analysis, we also report effects of finerenone on: 1) sustained $\geq 57\%$ eGFR decline or kidney failure; 2) eGFR slope; 3) changes in urine albumin/creatinine ratio (UACR).

Results: Among 6,001 participants, mean baseline eGFR was 62 ± 20 mL/min/1.73m²; 48% had eGFR < 60 mL/min/1.73m². Overall, 5,797 had baseline UACR data (median 18 [7,67] mg/g). Over 2.6 years median follow-up, the incidence of the composite kidney outcome ($\geq 50\%$ eGFR decline or kidney failure) was numerically, but non-significantly, higher for finerenone vs. placebo (75 vs. 55 events; HR 1.33; 95%CI 0.94, 1.89). Similar results were observed for the composite of $\geq 57\%$ eGFR decline or kidney failure (41 vs. 31 events; HR 1.28; 95%CI 0.80, 2.05), though the overall event frequency was relatively low. During the first 3 months, finerenone led to an acute decline in eGFR of -2.9 mL/min/1.73m² (95%CI $-3.4, -2.4$) but did not alter chronic (from 3 months) eGFR slope ($+0.2$ mL/min/1.73m²/year; 95%CI $-0.1, +0.4$), vs. placebo. The difference in total slope was -0.7 (95%CI -0.9 to -0.4) mL/min/1.73 m²/year. Finerenone

reduced UACR by 30% (95%CI 25%, 34%) over 6 months vs. placebo, an effect that persisted throughout follow-up. Finerenone reduced the risk of new-onset of micro- and macroalbuminuria by 24% (HR 0.76; 95%CI 0.68, 0.83) and 38% (HR 0.62; 95%CI 0.53, 0.73), respectively.

Conclusions: In FINEARTS-HF, a population at low risk of adverse kidney outcomes, finerenone did not significantly modify the kidney composite outcomes. Finerenone led to a greater reduction in initial eGFR, but did not result in a significant difference in chronic eGFR slope, vs. placebo. Finerenone led to early and sustained reductions in albuminuria and reduced the risk of new-onset micro- and macroalbuminuria.

Trial Registration

(Funded by Bayer; FINEARTS-HF ClinicalTrials.gov number, NCT04435626.)

Keywords: finerenone, HFmrEF, HFpEF, chronic kidney disease, safety

INTRODUCTION

Chronic kidney disease (CKD) affects around half of patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF).¹ CKD and HF frequently coexist with other metabolic conditions, such as type 2 diabetes mellitus (T2DM), contributing to a cardio-kidney-metabolic (CKM) overlap, with higher associated adverse outcomes compared with any individual condition alone.² Among patients with HFmrEF/HFpEF, the presence and magnitude of albuminuria is a potent predictor of both cardiovascular and kidney adverse outcomes.^{3,4}

Contemporary trials support the use of angiotensin receptor-neprilysin inhibitors (ARNI)⁵ (in select individuals) and sodium-glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular outcomes among patients with HFmrEF/HFpEF.^{6,7} In addition, both ARNI (sacubitril/valsartan) and SGLT2 inhibitors (dapagliflozin and empagliflozin) have beneficial effects on slowing the decline of estimated glomerular filtration rate (eGFR), compared with valsartan and placebo, respectively.⁷⁻¹⁰ However, in trials with SGLT2 inhibitors, as well among participants of TOPCAT (testing spironolactone, a steroidal mineralocorticoid receptor antagonist [MRA]), no treatment reductions in adverse kidney composite outcomes were observed, though effect estimates varied according to the definition of kidney disease progression.¹⁰

Finerenone, a non-steroidal MRA, has proven efficacy in reducing kidney disease progression and albuminuria in patients with CKD and T2DM,^{11,12} and was recently observed to lower the risk of the composite of HF events and cardiovascular death among patients with HFmrEF/HFpEF in the FINEARTS-HF trial.¹³ Here, in these prespecified analyses of FINEARTS-HF,

we explore the effects of finerenone on kidney outcomes (kidney disease progression, eGFR slope, and albuminuria).

METHODS

Data Sharing

Data are made available to qualified scientific and medical researchers through vivli.org. All requests will be reviewed by an independent scientific review panel and data provided according to the conditions laid out on <https://vivli.org/ourmember/bayer/>

Trial Design and Oversight

The trial design, analysis plan, and primary results of the FINEARTS-HF trial have been published.^{13,14} The trial protocol was approved by ethics committees or institutional review boards at all participating centers and all patients provided written informed consent. Trial oversight was provided by an independent data and safety monitoring committee. The first author wrote the first draft of the present manuscript. All authors contributed to revisions and made the collective decision to submit the manuscript for publication.

Study Patients

Briefly, FINEARTS-HF enrolled patients aged 40 years or older with symptomatic HF, LVEF $\geq 40\%$, evidence of structural heart disease (LV hypertrophy or left atrial enlargement within 12 months), and elevated serum concentration of natriuretic peptides. Notable exclusion criteria included: eGFR < 25 mL/min/1.73 m²; serum potassium > 5 mmol/L; hemoglobin < 10 g/dL; symptomatic hypotension (mean systolic BP < 90 mmHg); treatment with more than one ACEi, ARB, or ARNI (or two simultaneously) at randomization. Patients were

randomized in a 1:1 fashion to finerenone titrated to either 20mg or 40mg (depending on baseline eGFR) versus matching placebo.

Kidney Outcomes

A key prespecified secondary outcome was a kidney composite of either: a sustained $\geq 50\%$ decline in eGFR from baseline, sustained decline in eGFR to <15 mL/min/1.73m², or the initiation of long-term dialysis or kidney transplantation (the latter two adjudicated by a blinded clinical endpoints committee). In the present analyses, a prespecified kidney composite was also considered, consisting of either: a sustained $\geq 57\%$ decline in eGFR from baseline, sustained decline in eGFR to <15 mL/min/1.73 m², or the initiation of long-term dialysis or kidney transplantation. To qualify as sustained, a repeat central laboratory confirmation was required at least 4 weeks after the initial measurement; if no confirmatory sample was available, events were only counted if the patient had subsequently died or initiated kidney replacement therapy.

Other prespecified kidney outcomes in the present analyses include: the change in eGFR from baseline; the mean rate of change in eGFR (total slope and its subcomponents, acute [baseline to 3 months] and chronic [3 months to end of study] slope); and the change in UACR from baseline. The development of new-onset microalbuminuria (urine albumin:creatinine ratio [UACR] ≥ 30 mg/g) and macroalbuminuria (UACR ≥ 300 mg/g) were prespecified outcomes among those with baseline UACR) <30 and <300 mg/g, respectively.

Safety Outcomes

Safety analyses were performed among those who took at least one dose of study drug and considered events that occurred during treatment or up to 3 days after permanent drug

discontinuation. Effects of finerenone versus placebo were examined on the incidence of at least 1 adverse event, at least 1 serious adverse event, hyperkalemia, elevations in serum creatinine, and systolic blood pressure <100 mmHg, according to categories of the baseline eGFR (≥ 60 , $45-60$, <60 mL/min/1.73m²).

Statistical Analysis

Summary data were reported as mean (\pm standard deviation [SD]) when normally distributed, median [25th-75th percentile] when non-normally distributed, and as frequencies and percentages for categorical data. The Student's t-test, Wilcoxon Rank Sum, or chi-square tests were used to assess for differences between baseline variables by eGFR category (≥ 60 , 45 to <60 , <45 mL/min/1.73 m²), according to data distribution. Incidence rates and 95% confidence intervals were calculated per 100 patient-years of follow-up.

Cox proportional hazards models, stratified by geographic region and left ventricular ejection fraction (<60 or $\geq 60\%$), were fit to assess the effect of finerenone vs. placebo on the kidney composite outcomes. Changes in eGFR (continuous) and UACR (using geometric means) over time were assessed with repeated measures mixed effect models, using available data from randomization, 1, 3, 6, 12, 16, 20, 24, 28, 32, and 36 months. Models were adjusted for treatment assignment, trial visit, geographic region, left ventricular ejection fraction (<60 or $\geq 60\%$), the interaction between treatment assignment and visit. Intercepts and slopes over time were allowed to vary randomly between patients via the inclusion of patient and time as random effects. A single-slope model was used to estimate the overall slope from Month 0 to Month 36, while a two-slope model with a specified change-point at Month 3 was used to estimate the acute slope (Month 0 to Month 3) and the chronic slope (Month 3 to Month 36).

New-onset microalbuminuria and macroalbuminuria were assessed using Cox proportional hazards models stratified for the same factors as above and restricted to those with UACR < 30 and <300 mg/g at baseline, respectively.

For the main kidney composite outcome, interaction terms were included in separate models to test if the treatment effect differed according to baseline CKD categories, history of diabetes, or category of baseline albuminuria (<300 vs. ≥300 mg/g).

In the prespecified hierarchical testing plan, the kidney composite outcome was the fourth of the secondary outcomes to be tested (following total worsening HF events, change in KCCQ total symptom score, and improvement in NYHA class). As the difference in NYHA class was non-significant, the subsequent testing of the main kidney composite was deemed exploratory.¹³ All present analyses were performed at an alpha level of 0.05, without correction for multiple hypothesis testing, using Stata MP (version 18.0, Stata Corp., College Station, Texas).

RESULTS

Patients

At baseline, among 6,001 participants the mean eGFR was 62 ± 20 mL/min/1.73 m², with 3,113 (52%) having an eGFR ≥60 mL/min/1.73 m²; 1,556 (26%) having an eGFR 45-<60 mL/min/1.73 m², and 1,332 (22%) having an eGFR <45 mL/min/1.73 m². Baseline characteristics were well balanced according to randomized treatment assignments within these eGFR categories (**Table 1**).

Kidney Composite Outcome

The overall frequency of the kidney composite outcome (sustained ≥50% decline in eGFR, sustained eGFR decline <15 mL/min/1.73 m², or kidney failure) was low, occurring in 55

(1.8%) of 2,998 patients assigned to placebo and 75 (2.5%) of 3,003 patients assigned to finerenone (HR 1.33; 95%CI 0.94, 1.89; **Table 2**). Of the composite components, the majority of events were related to the $\geq 50\%$ decline in eGFR from baseline (52 and 73 events in those randomized to placebo and finerenone, respectively). Only 6 patients in the placebo group and 7 patients in the finerenone group developed kidney failure requiring dialysis.

Treatment effects on the kidney composite outcome did not significantly differ according to categories of baseline eGFR (P-interaction=0.18; Supplemental Table 1), or by categories of baseline UACR (<300 vs. ≥ 300 mg/g) or history of diabetes (P-interaction=0.58 and 0.31, respectively; Supplemental Table 2).

The overall frequency of the kidney composite outcome (sustained $\geq 57\%$ decline in eGFR, sustained eGFR decline < 15 mL/min/1.73 m², or kidney failure) was low, occurring in 31 (1.0%) of 2,998 patients assigned to placebo and 41 (1.4%) of 3,003 patients assigned to finerenone (HR 1.28; 95%CI 0.80, 2.05; **Table 2**).

eGFR changes over time

An initial acute decline in eGFR was observed in those assigned to finerenone between baseline and month 3 (-3.0; 95%CI -3.4 to -2.7 mL/min/1.73 m²), compared with those assigned to placebo (-0.1; 95%CI -0.5 to +0.2 mL/min/1.73 m²), with a mean difference of -2.9 (95%CI -3.4 to -2.4) mL/min/1.73 m². Between month 3 through the end of the trial, the mean change in eGFR was -0.9 (95% CI -1.1 to -0.7) mL/min/1.73 m² per year for those assigned to finerenone, compared with -1.1 (95% CI -1.3 to -0.9) mL/min/1.73 m² per year for those assigned to placebo, with a mean difference of 0.2 (95% CI -0.1 to +0.4) mL/min/1.73 m² per year. The mean

difference for total slope was -0.7 (95%CI -0.9 to -0.4) mL/min/1.73 m². Changes in mean eGFR over time are displayed graphically in Figure 1.

UACR changes over time and the development of micro- and macroalbuminuria

Overall, 5,797 participants had baseline UACR data, of which 3,511 (61%) had UACR <30 mg/g; 1,712 (30%) had UACR 30- <300 mg/g; and 574 (10%) had UACR ≥300 mg/g. The median baseline UACR was 18 [7, 67] mg/g. Finerenone led to an early reduction in UACR, which was 30% (95%CI 25%, 34%) lower at six months compared with placebo, and remained reduced throughout the remainder of the follow-up period (**Figure 2**).

Among those with baseline UACR <300 mg/g, macroalbuminuria (UACR ≥300 mg/g) developed in 386 (15%) of 2,614 patients assigned to placebo and 250 (10%) of 2,609 assigned to finerenone (HR 0.62; 95%CI 0.53, 0.73; Figure 3). This treatment effect was consistent according to baseline eGFR (P-interaction=0.51 and 0.28 for continuous (linear) eGFR and categories of eGFR, respectively; Supplemental Table 1).

Among those with baseline UACR <30 mg/g, micro- or macroalbuminuria (UACR ≥30 or UACR ≥300 mg/g) developed in 884 (51%) of 1,746 patients assigned to placebo and 742 (42%) of 1,765 assigned to finerenone (HR 0.76; 95%CI 0.68, 0.83; **Figure 3**). The treatment effect appeared to be consistent according to baseline eGFR (P-interaction=0.09 and 0.08 for continuous (linear) eGFR and categories of eGFR, respectively; Supplemental Table 1).

Safety Outcomes

Serious adverse events, elevations in serum creatinine ≥3.0 mg/dL, and adverse events related to hyperkalemia were more frequent among patients in lower (vs. eGFR ≥60 mL/min/1.73 m²) categories of baseline eGFR (**Table 3**).

Among all categories of baseline eGFR, the frequency of serious adverse events was broadly similar between randomized treatment groups. Among all categories of baseline eGFR, the frequency of hyperkalemia was higher in those assigned to finerenone than those assigned to placebo, but few events led to hospitalization: 5 (0.3%) vs 1 (0.1%) among those with eGFR ≥ 60 mL/min/1.73 m²; 3 (0.4%) vs 2 (0.3%) among those with eGFR 45-<60 mL/min/1.73 m²; 8 (1.2%) vs 3 (0.4%) among those with eGFR <45 mL/min/1.73 m² (**Table 3**). There were no deaths related to hyperkalemia in either arm. Any systolic BP <100 mmHg was more common in finerenone compared with placebo across all categories of baseline eGFR (**Table 3**).

DISCUSSION

Among patients with HFmrEF/HFpEF in the FINEARTS-HF trial, who were at relatively low risk of adverse clinical kidney outcomes, the frequency of kidney composite events was numerically higher, but not statistically significantly different, for finerenone versus placebo. Finerenone caused an initial decline in eGFR (and total slope), but did not alter the longer-term “chronic” eGFR slope, compared with placebo. The frequency of hyperkalemia and elevation in serum creatinine was higher for patients treated with finerenone, but rarely led to discontinuation of treatment. Finerenone reduced albuminuria and the development of new-onset micro- and macroalbuminuria.

Albuminuria is a potent predictor of adverse outcomes across a broad spectrum of patients, including those with HFmrEF/HFpEF,^{3,4} while in post hoc analyses of trials with patients with CKD and T2DM (which included patients with UACR >30 mg/g), reductions in UACR were estimated to mediate 84% and 37% of the treatment effect of finerenone vs. placebo on the kidney and cardiovascular outcomes, respectively.¹⁵ In the present analyses, finerenone caused

an early reduction in albuminuria that persisted throughout the duration of follow-up. The proportional magnitude of UACR lowering was similar to that observed in the trials of patients with CKD and T2DM, and is thought to be related to lowering of intraglomerular pressure.^{12,16}

In two large placebo-controlled trials (FIGARO-DKD or FIDELIO-DKD), finerenone lowered the risk of adverse kidney composite outcomes (sustained $\geq 40/57\%$ eGFR decline, kidney failure, or death from kidney causes) among patients with CKD, T2DM, and albuminuria.^{11,12} Based on these results, finerenone has received indications to reduce the risk of sustained decline in eGFR and end-stage kidney disease in adult patients with CKD associated with T2DM. However, similar to post hoc analyses of steroidal mineralocorticoid receptor antagonists among patients with HFrEF or HFpEF,^{10,17,18} in the present analyses, finerenone did not alter the occurrence of the kidney composite outcomes, nor the longer-term 'chronic' (from 3 months) slope in eGFR.

There are several potential reasons for the lack of observed benefits on eGFR-based outcomes.¹⁹ First, patients enrolled in FINEARTS-HF were at lower overall risk of adverse kidney outcomes, compared with those enrolled in FIGARO-DKD or FIDELIO-DKD. For example, higher degrees of albuminuria and the presence of T2DM are known risk factors for CKD progression.²⁰ Patients in FINEARTS-HF had a median baseline UACR concentration of 18 mg/g, compared with 852 mg/g in FIDELIO-DKD and 308 mg/g in FIGARO-DKD.^{11,12} Further, T2DM was not an inclusion criterion in FINEARTS-HF and was present in only 41% of patients at baseline. For further context, the differences in risk profiles are evident from the differences in the overall frequency of a harmonized kidney composite outcome (133 in FINEARTS-HF, 380 in FIGARO-DKD, 729 in FIDELIO-DKD).²¹

Second, the initiation of finerenone is known to cause an initial decline in eGFR that is sustained throughout the duration of treatment.^{11,12} In the absence of an off-drug measurement of eGFR, an excessive initial eGFR decline in select patients could contribute to a higher likelihood of meeting the threshold of a sustained decline in eGFR of $\geq 50\%$ from baseline. In an attempt to mitigate the influence of excessive initial eGFR declines, higher thresholds have been incorporated in prior trials (e.g., sustained $\geq 57\%$ eGFR decline), meaning that greater decrements in kidney function are needed to reach the outcome definition. Interestingly, more potent risk reductions in the kidney outcomes for finerenone vs. placebo were noted in the aforementioned trials (FIDELIO-DKD and FIGARO-DKD) with this more restrictive definition.^{11,12,21}

Third, the duration of follow-up in HF trials may be shorter than that of CKD progression trials, where kidney outcomes tend to accumulate much later.²² Combined with a lower overall rate of CKD progression (the observed eGFR decline in the placebo arm of FINEARTS-HF was only 1.1 mL/min/1.73 m²/year, similar to that expected with aging alone), a shorter duration of follow-up provides less opportunity to 'overcome' the initial decline in eGFR observed with finerenone. For context, the rate of decline in the placebo arm in FINEARTS-HF was even lower than that of other contemporary trials among patients with HFmrEF/HFpEF (1.5 mL/min/1.73 m²/year in DELIVER and 2.6 mL/min/1.73 m²/year in EMPEROR-Preserved),^{9,23} perhaps reflecting greater utilization of background nephroprotective therapy in more contemporary populations. The tendency for kidney outcomes to occur later in the disease course, particularly in this HFmrEF/HFpEF cohort, also predisposes to the issue of competing risks,

where fatal events that occur earlier in the disease course preclude the future development of adverse kidney outcomes.

Finerenone resulted in a higher frequency of hyperkalemia than placebo, although the overall number of severe events (e.g., leading to hospitalization) was low and there were no deaths related to hyperkalemia observed in follow-up. Not surprisingly, the frequency of hyperkalemic events was higher among those with lower baseline eGFR (among both treatment arms). While a prior Phase II trial suggested a potentially lower risk of hyperkalemia and worsening renal function for finerenone vs. spironolactone, FINEARTS-HF was a placebo-controlled trial, precluding a direct comparison of finerenone with other MRAs.²⁴ Overall, the present results highlight the need for regular monitoring of such patients upon initiation of therapies that can increase serum potassium concentration.

The strengths of our analyses include the examination of prespecified kidney outcomes that required confirmatory measurements of eGFR, all collected in the setting of a large, robust, placebo-controlled randomized trial. The main limitations of our analyses include the low/modest number of kidney composite outcomes, the relatively short follow-up, the inability to assess off-drug eGFR measurements, and the fact that the included patients were at relatively low risk of developing longer-term adverse kidney outcomes. Certain sub-group analyses of interest, e.g., baseline use of SGLT2 inhibitors, were precluded due to small numbers of patients.

In summary, in this prespecified analysis to examine kidney outcomes among patients with HFmrEF/HFpEF, finerenone did not alter eGFR-based kidney outcomes compared with placebo, but did lower albuminuria and reduce the risk of new-onset micro- and

macroalbuminuria. Given the benefits of finerenone to lower the risk of the primary outcome of cardiovascular death and total HF events,¹³ these data provide ancillary information for patients and clinicians on the expected kidney-specific effects of finerenone among patients with HFmrEF/HFpEF.

Journal Pre-proof

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Figure Legends

Figure 1. Change in eGFR over 36 months. Means for the estimated glomerular filtration rate (eGFR) over a period of 36 months. The I bars indicate 95% confidence intervals.

Figure 2. Change in eGFR over 36 months. Means for the percentage decline in the urine albumin:creatinine ratio over a period of 36 months. The I bars indicate 95% confidence intervals.

Figure 3. Effect of finerenone versus placebo on new-onset microalbuminuria (Panel A) and macroalbuminuria (Panel B). Kaplan-Meier estimates for the development of new-onset microalbuminuria (urine albumin:creatinine ratio [UACR] ≥ 30 mg/g) among those with baseline UACR < 30 mg/g macroalbuminuria (UACR ≥ 300 mg/g) among those with baseline UACR < 300 mg/g.

Table 1. Characteristics according to category of CKD and randomized treatment assignment

	eGFR ≥ 60 mL/min/1.73 m ²		eGFR 45 to < 60 mL/min/1.73 m ²		eGFR < 45 mL/min/1.73 m ²	
	Placebo n=1561	Finerenone n=1552	Placebo n=754	Finerenone n=802	Placebo n=683	Finerenone n=649
Age, years	68 \pm 10	69 \pm 10	75 \pm 8	74 \pm 8	77 \pm 8	77 \pm 8
Female, n(%)	643 (41.2%)	637 (41.0%)	375 (49.7%)	400 (49.9%)	359 (52.6%)	318 (49.0%)
<u>Race, n(%)</u>						
Asian	255 (16.3%)	252 (16.2%)	118 (15.6%)	122 (15.2%)	126 (18.4%)	123 (19.0%)
Black	22 (1.4 %)	28 (1.8 %)	9 (1.2 %)	15 (1.9 %)	8 (1.2 %)	6 (0.9 %)
Other	39 (2.5 %)	47 (3.0 %)	27 (3.6 %)	22 (2.7 %)	25 (3.7 %)	22 (3.4 %)
White	1245 (79.8%)	1225 (78.9%)	600 (79.6%)	643 (80.2%)	524 (76.7%)	498 (76.7%)
<u>Geographic Region, n(%)</u>						
Asia	249 (16.0%)	250 (16.1%)	117 (15.5%)	121 (15.1%)	124 (18.2%)	122 (18.8%)
Eastern Europe	794 (50.9%)	762 (49.1%)	324 (43.0%)	346 (43.1%)	203 (29.7%)	221 (34.1%)
Latin America	175 (11.2%)	179 (11.5%)	67 (8.9 %)	77 (9.6 %)	77 (11.3%)	66 (10.2%)
North America	94 (6.0 %)	96 (6.2 %)	76 (10.1%)	80 (10.0%)	66 (9.7 %)	59 (9.1 %)
Western Europe, Oceania and Others	249 (16.0%)	265 (17.1%)	170 (22.5%)	178 (22.2%)	213 (31.2%)	181 (27.9%)
Any prior hospitalization for heart failure, n(%)	913 (58.5%)	905 (58.3%)	453 (60.1%)	474 (59.1%)	456 (66.8%)	418 (64.4%)
Systolic blood pressure, mmHg	130 \pm 15	130 \pm 15	130 \pm 16	129 \pm 15	128 \pm 16	130 \pm 16
Body-mass index, kg/m²	30.2 \pm 6.1	29.7 \pm 6.0	30.2 \pm 6.3	30.4 \pm 6.3	29.4 \pm 6.0	29.7 \pm 6.1
Serum creatinine, mg/dL	0.9 \pm 0.2	0.9 \pm 0.2	1.2 \pm 0.2	1.2 \pm 0.2	1.6 \pm 0.5	1.6 \pm 0.3
eGFR, mL/min/1.73 m²	78 \pm 12	77 \pm 12	53 \pm 4	53 \pm 4	36 \pm 6	36 \pm 6
Urine albumin:creatinine ratio, mg/g	14 [6, 45]	14 [5, 45]	20 [7, 77]	19 [8, 75]	31 [11, 148]	36 [11, 176]
Serum potassium, mmol/L	4.3 \pm 0.5	4.4 \pm 0.4	4.4 \pm 0.5	4.4 \pm 0.5	4.4 \pm 0.5	4.4 \pm 0.5
Left ventricular ejection fraction, (%)	52 \pm 8	52 \pm 8	53 \pm 8	53 \pm 8	53 \pm 8	54 \pm 8
NT-proBNP, pg/mL	766 [338 , 1486]	844 [372 , 1529]	1219 [535 , 2339]	1152 [536 , 2030]	1581 [790 , 3025]	1638 [784 , 2946]
History of hypertension, n(%)	1370 (87.8%)	1319 (85.0%)	687 (91.1%)	731 (91.1%)	628 (91.9%)	590 (90.9%)
History of Diabetes, n(%)	583 (37.3%)	556 (35.8%)	301 (39.9%)	338 (42.1%)	338 (49.5%)	323 (49.8%)
History of stroke, n(%)	161 (10.3%)	154 (9.9 %)	88 (11.7%)	105 (13.1%)	104 (15.2%)	96 (14.8%)

History of myocardial infarction, n(%)	411 (26.3%)	446 (28.7%)	187 (24.8%)	188 (23.4%)	159 (23.3%)	150 (23.1%)
Beta-blocker, n(%)	1342 (86.0%)	1316 (84.8%)	643 (85.3%)	688 (85.8%)	569 (83.3%)	537 (82.7%)
Angiotensin-converting enzyme inhibitor, n(%)	616 (39.5%)	613 (39.5%)	257 (34.1%)	275 (34.3%)	199 (29.1%)	195 (30.0%)
Angiotensin-receptor blocker, n(%)	521 (33.4%)	503 (32.4%)	287 (38.1%)	316 (39.4%)	247 (36.2%)	228 (35.1%)
Angiotensin receptor-neprilysin inhibitor, n(%)	154 (9.9%)	141 (9.1%)	56 (7.4%)	60 (7.5%)	47 (6.9%)	55 (8.5%)
Sodium-glucose cotransporter 2 inhibitor, n(%)	188 (12.0%)	180 (11.6%)	103 (13.7%)	116 (14.5%)	133 (19.5%)	97 (14.9%)
Loop diuretic, n(%)	1329 (85.1%)	1329 (85.6%)	662 (87.8%)	685 (85.4%)	630 (92.2%)	604 (93.1%)
Thiazide diuretic, n(%)	225 (14.4%)	231 (14.9%)	110 (14.6%)	130 (16.2%)	67 (9.8%)	68 (10.5%)

Plus-minus values are means \pm SD; non-normally distributed variables are presented as medians [25th, 75th percentiles]. Percentages may not total 100 because of rounding.

Abbreviations: eGFR, estimated glomerular filtration rate; NT-proBNP N-terminal pro-B-type natriuretic peptide. Race was determined by the patient.

Body-mass index is the weight in kilograms divided by the square of the height in meters.

Significant differences were noted for BMI and baseline eGFR in eGFR category >60 mL/min/1.73 m²; systolic BP and baseline SGLT2i use in eGFR category <45 mL/min/1.73 m²

Table 2. Treatment effect on kidney outcomes

Outcome	Placebo	Finerenone
Composite kidney outcome (inc. $\geq 50\%$ eGFR decline)		
No. events/No. patients (%)	55/2998 (1.8%)	75/3003 (2.5%)
Rate/100 PY (95% CI)	0.9 (0.7, 1.1)	1.2 (0.9, 1.5)
Hazard Ratio (95%CI)	1.33 (0.94, 1.89)	
$\geq 50\%$ eGFR decline		
No. events/No. patients (%)	52/2998 (1.7%)	73/3003 (2.4%)
eGFR decline < 15 mL/min/1.73 m²		
No. events/No. patients (%)	12/2998 (0.4%)	25/3003 (0.8%)
Dialysis initiation		
No. events/No. patients (%)	6/2998 (0.2%)	7/3003 (0.2%)
Composite kidney outcome (inc. $\geq 57\%$ eGFR decline)		
No. events/No. patients (%)	31/2998 (1.0%)	41/3003 (1.4%)
Rate/100 PY (95% CI)	0.5 (0.3, 0.7)	0.6 (0.5, 0.9)
Hazard Ratio (95%CI)	1.28 (0.80, 2.05)	

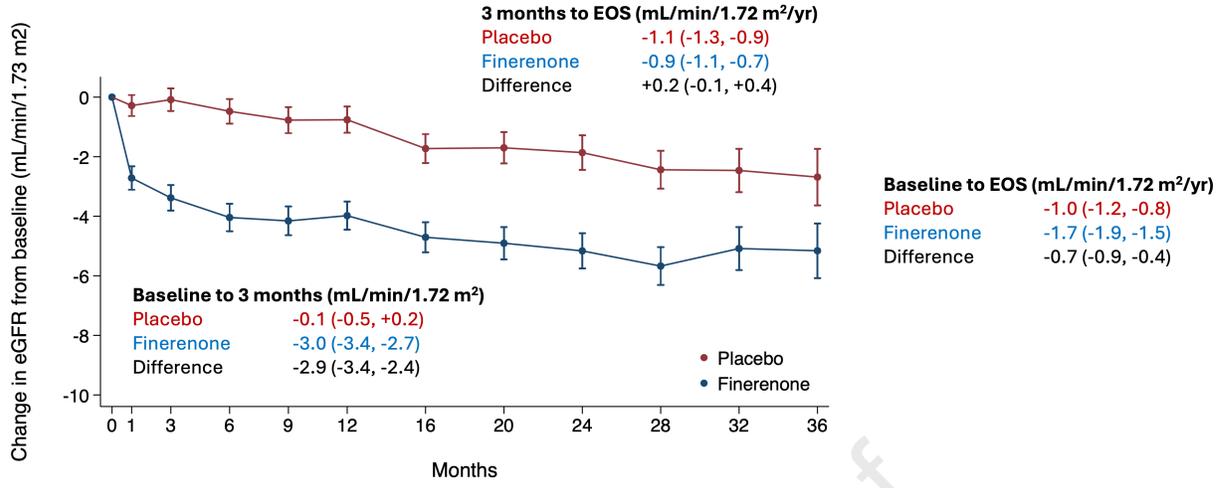
Composite kidney outcome includes: sustained $\geq 50\%$ or $\geq 57\%$ eGFR decline from baseline, sustained eGFR decline < 15 mL/min/ 1.73 m²; kidney failure.

Abbreviations: PY, patient years; CI, confidence interval.

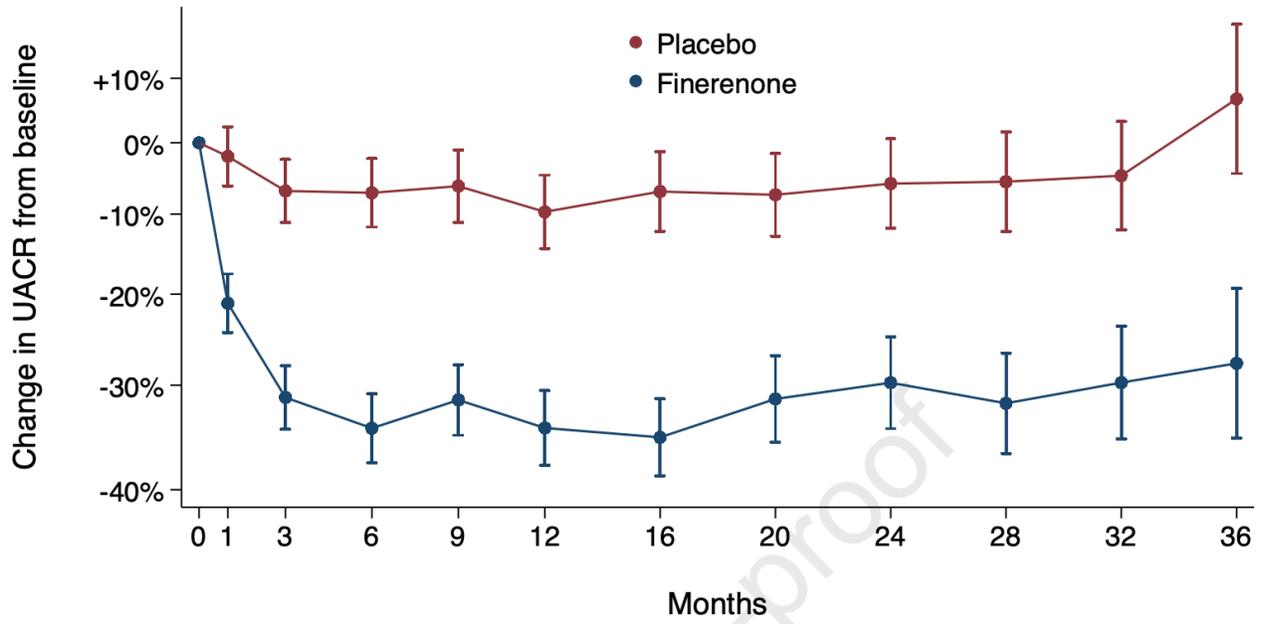
Table 3. Safety outcomes according to category of CKD and randomized treatment assignment

	eGFR ≥ 60 mL/min/1.73 m ²		eGFR 45 to <60 mL/min/1.73 m ²		eGFR <45 mL/min/1.73 m ²		All patients	
	Placebo n=1557	Finerenone n=1547	Placebo n=754	Finerenone n=800	Placebo n=682	Finerenone n=646	Placebo n=2993	Finerenone n=2993
Any serious adverse event	552 (35.5%)	498 (32.2%)	344 (45.6%)	341 (42.6%)	317 (46.5%)	318 (49.2%)	1213 (40.5%)	1157 (38.7%)
Serum creatinine ≥ 3.0 mg/dL	2 (0.1%)	11 (0.7%)	5 (0.7%)	5 (0.6%)	27 (4.2%)	41 (6.7%)	34 (1.2%)	57 (2.0%)
Acute kidney injury	18 (1.2%)	31 (2.0%)	21 (2.8%)	26 (3.2%)	25 (3.7%)	54 (8.4%)	64 (2.1%)	111 (3.7%)
Acute kidney injury that led to hospitalization	7 (0.4%)	8 (0.5%)	7 (0.9%)	9 (1.1%)	11 (1.6%)	31 (4.8%)	25 (0.8%)	48 (1.6%)
Investigator reported hyperkalemia	29 (1.9%)	97 (6.3%)	45 (6.0%)	79 (9.9%)	51 (7.5%)	113 (17.5%)	125 (4.2%)	289 (9.7%)
Serum potassium >5.5 mmol/L	86 (5.7%)	175 (11.6%)	55 (7.6%)	118 (15.1%)	58 (8.9%)	120 (19.7%)	199 (6.9%)	413 (14.3%)
Serum potassium >6.0 mmol/L	16 (1.1%)	36 (2.4%)	12 (1.7%)	27 (3.5%)	13 (2.0%)	23 (3.8%)	41 (1.4%)	86 (3.0%)
Serum potassium >7.0 mmol/L	5 (0.3%)	8 (0.5%)	1 (0.1%)	6 (0.8%)	0 (0.0%)	2 (0.3%)	6 (0.2%)	16 (0.6%)
Hyperkalemia that led to hospitalization	1 (0.1%)	5 (0.3%)	2 (0.3%)	3 (0.4%)	3 (0.4%)	8 (1.2%)	6 (0.2%)	16 (0.5%)
Systolic blood pressure <100 mmHg	164 (10.8%)	270 (17.9%)	94 (12.9%)	150 (19.2%)	103 (15.7%)	118 (19.1%)	361 (12.4%)	538 (18.5%)

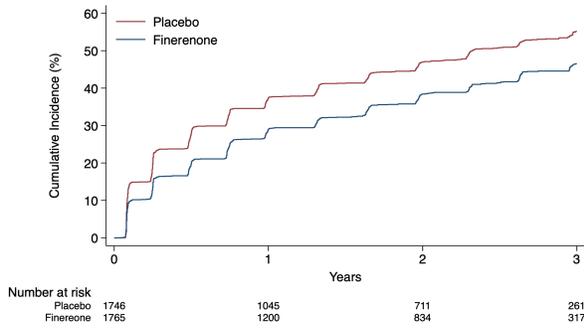
Reported events are those that occurred in patients who had received at least one dose of finerenone or placebo and occurred during treatment or up to 3 days after permanent discontinuation of finerenone or placebo (n=5986). Data reported on creatinine, potassium, and systolic blood pressure were further restricted to patients with at least one assessment (5785, 5787, and 5815 patients, respectively).



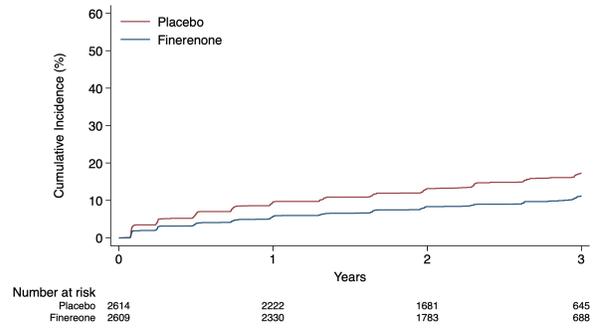
Change in UACR from baseline over 36 months



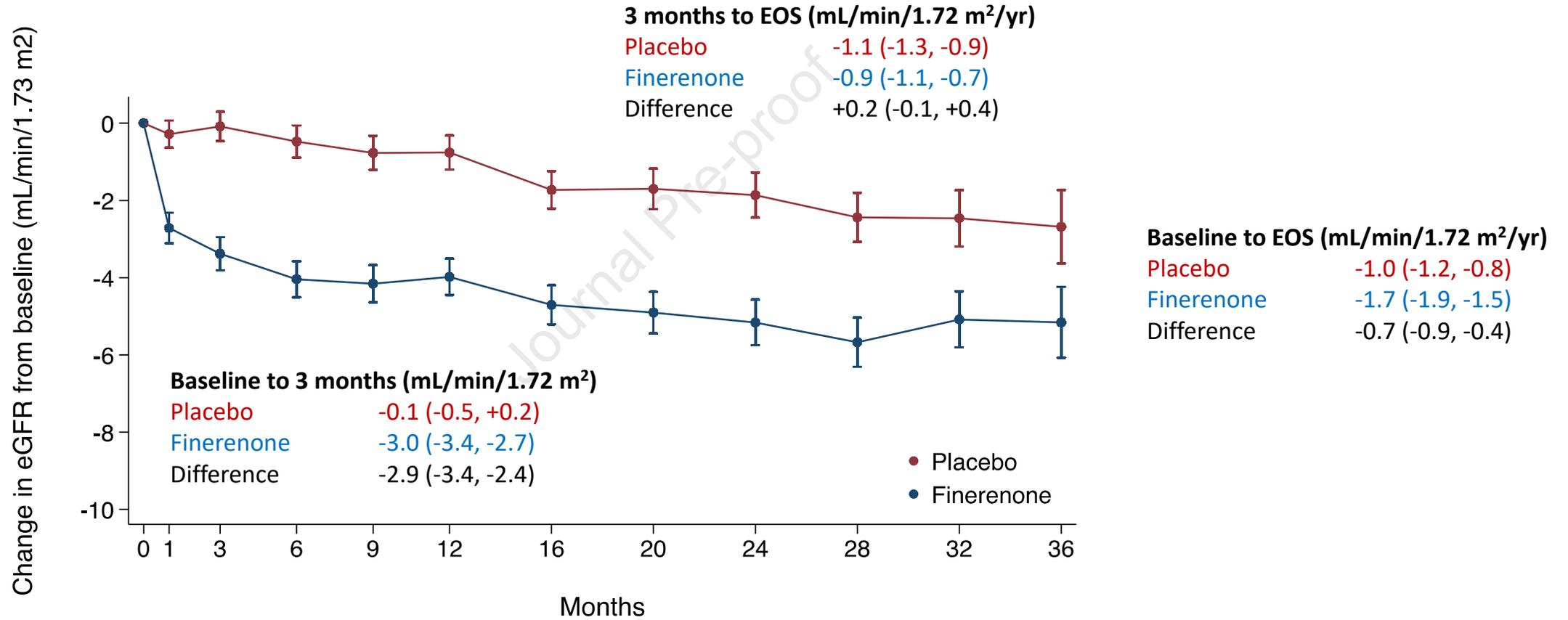
A New-onset microalbuminuria



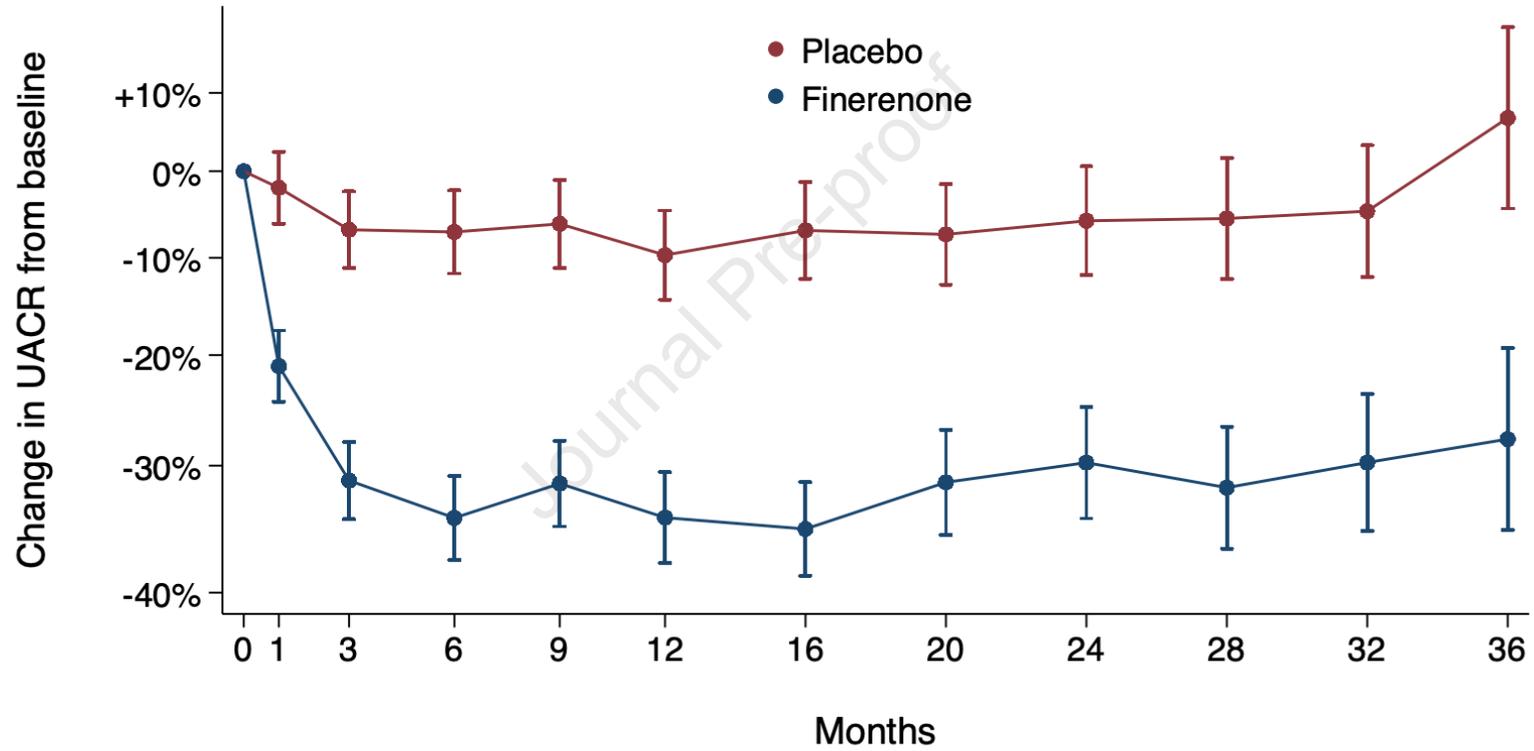
B New-onset macroalbuminuria



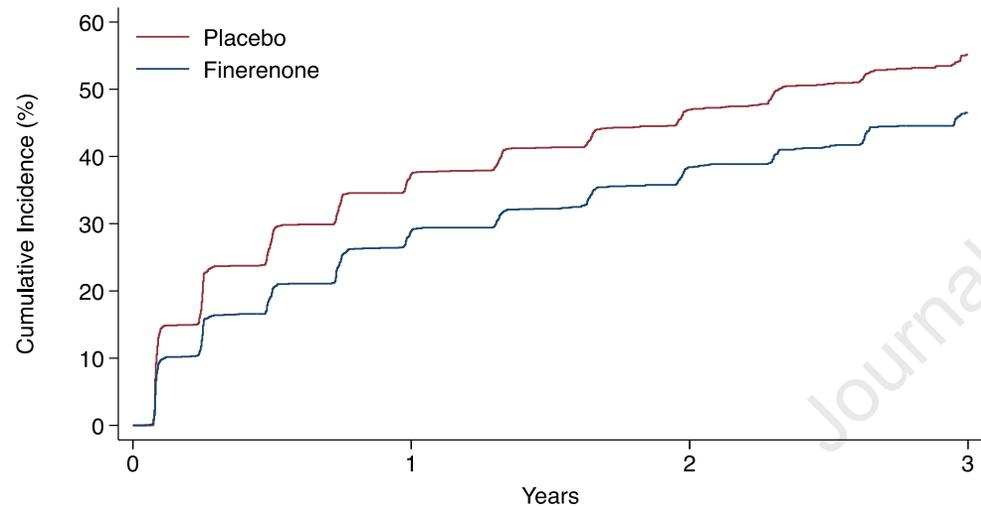
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Change in UACR from baseline over 36 months



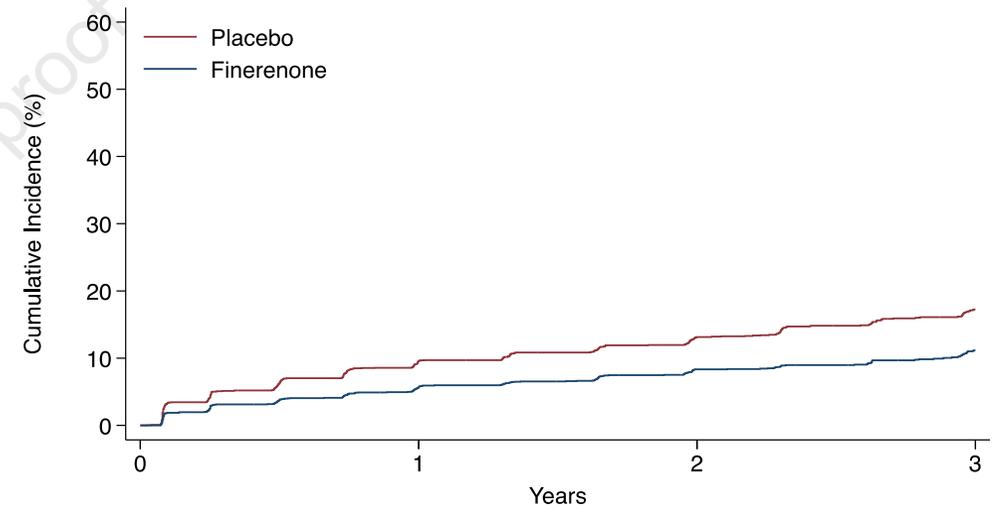
A New-onset microalbuminuria



Number at risk

Placebo	1746	1045	711	261
Finerenone	1765	1200	834	317

B New-onset macroalbuminuria



Number at risk

Placebo	2614	2222	1681	645
Finerenone	2609	2330	1783	688

Supplementary Table 1. Treatment effect on kidney outcomes according to category of CKD

Outcome	eGFR ≥ 60 mL/min/1.73 m ²		eGFR 45 to < 60 mL/min/1.73 m ²		eGFR < 45 mL/min/1.73 m ²		P-interaction
	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	
Composite kidney outcome (inc. $\geq 50\%$ eGFR decline)							
No. events (%)	27/1561 (2%)	27/1552 (2%)	12/754 (2%)	19/802 (2%)	16/683 (2%)	29/649 (4%)	
Rate/100 PY (95% CI)	0.8 (0.5, 1.1)	0.8 (0.5, 1.1)	0.7 (0.4, 1.3)	1.1 (0.7, 1.7)	1.2 (0.7, 2.0)	2.3 (1.6, 3.3)	
Hazard Ratio (95%CI)	0.92 (0.53, 1.58)		1.50 (0.72, 3.09)		2.00 (1.08, 3.70)		0.18
$\geq 50\%$ eGFR decline							
No. events (%)	27/1561 (2%)	27/1552 (2%)	12/754 (2%)	19/802 (2%)	13/683 (2%)	27/649 (4%)	
eGFR decline < 15 mL/min/1.73 m²							
No. events (%)	0/1561 (0%)	2/1552 (0%)	0/754 (0%)	3/802 (0%)	12/683 (2%)	20/649 (3%)	
Dialysis initiation							
No. events (%)	-	-	0/754 (0%)	1/802 (0%)	6/683 (1%)	6/649 (1%)	
Macroalbuminuria (≥ 300 mg/g)							
No. events (%)	192/1402 (14%)	110/1414 (8%)	93/672 (14%)	71/695 (10%)	101/540 (19%)	69/500 (14%)	
Rate/100 PY (95% CI)	6.0 (5.2, 6.9)	3.2 (2.7, 3.9)	6.4 (5.2, 7.8)	4.4 (3.5, 5.6)	9.1 (7.5, 11.1)	6.6 (5.2, 8.4)	
Hazard Ratio (95%CI)	0.55 (0.43, 0.69)		0.69 (0.51, 0.94)		0.74 (0.54, 1.00)		0.28
Micro- or macroalbuminuria (≥ 30 mg/g)							
No. events (%)	477/1004 (48%)	367/1018 (36%)	226/429 (53%)	236/465 (51%)	181/313 (58%)	139/282 (49%)	
Rate/100 PY (95% CI)	27.9 (25.5, 30.5)	18.7 (16.9, 20.7)	35.4 (31.1, 40.4)	30.8 (27.1, 34.9)	42.6 (36.8, 49.2)	31.7 (26.9, 37.5)	
Hazard Ratio (95%CI)	0.69 (0.60, 0.79)		0.90 (0.75, 1.09)		0.78 (0.62, 0.98)		0.08

Supplementary Table 2. Treatment effect on kidney composite outcome according to category of baseline UACR and diabetes

Outcome	UACR <300 mg/g		UACR ≥300 mg/g		No diabetes		Diabetes	
	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone
Composite kidney outcome (inc. ≥50% eGFR decline)								
No. events (%)	34/2614 (1.3%)	44/2609 (1.7%)	19/282 (6.7%)	30/292 (10.3%)	26/1776 (1.5%)	30/1786 (1.7%)	29/1222 (2.4%)	45/1217 (3.7%)
Rate/100 PY (95% CI)	0.6 (0.4, 0.8)	0.8 (0.6, 1.0)	3.7 (2.4, 5.8)	5.4 (3.8, 7.8)	0.7 (0.5, 1.0)	0.8 (0.5, 1.1)	1.1 (0.8, 1.6)	1.8 (1.3, 2.4)
Hazard Ratio (95%CI)	1.26 (0.80, 1.98)		1.52 (0.84, 2.73)		1.09 (0.64, 1.85)		1.56 (0.98, 2.50)	

P-interaction for treatment effect according to categories of UACR (<300 or ≥300 mg/g) history of diabetes was 0.58 and 0.31, respectively.