PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials
AUTHORS	Bansal, Shweta; Canziani, M. E. F.; Birne, Rita; Anker, Stefan; Bakris, George; Filippatos, Gerasimos; Rossing, Peter; Ruilope, Luis M; Farjat, Alfredo; Kolkhof, Peter; Lage, Andrea; Brinker, Meike; Pitt, B

VERSION 1 – REVIEW

REVIEWER	Chávez-Iñiguez, Jonathan University of Guadalajara, Nephrology
REVIEW RETURNED	19-Jun-2023

GENERAL COMMENTS	Enthusiastically reviewed the post hoc study of the FIDELITY study, this time the authors intend to demonstrate the effect of finerenone in subgroups of patients according to their age and sex. An interesting analysis with great relevance in current nephrology, which has important merits, but also aspects that I consider can improve its quality before considering its publication. 1.- I suggest that in Abstract the magnitude of the decrease in CV events be added, commented by the HR obtained in each objective. 2.- At the conclusion of the Abstract, the authors comment that finerenone is "safe", I think that phrase should not be included in this section, since the study was not designed to demonstrate safety, the title specifies CV results. 3.- In the results section, I suggest eliminating the numerator and denominator (example: 9,088/13,026), it is repetitive and necessary, just leave the percentage. 4.-How did you identify menopausal patients? Please explain the definition in Methods. 5.-Annotate the mean eGFR and median albuminuria values in the manuscript. 6.-Add in methods section that the CONSORT guide has been followed. 7.- If allowed by the Editorial group of the journal, it would be appropriate to make a Graphic Abstract that summarizes the results. 8.- In conclusions, I think that the positive effect that finerenone had specifically in men >75 years should be mentioned, data that I find very relevant.

REVIEWER	Ghosh, Alokananda

	The George Washington University Biostatistics Center, Biostatistics and Bioinformatics
REVIEW RETURNED	13-Oct-2023

GENERAL COMMENTS	This work extends the results of FIDELITY to examine whether the cardiovascular and kidney benefits, as well as the safety profile of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist (MRA), are maintained across 2 key subgroups: age and sex. Age is modeled as a categorical variable. The manuscript articulates why this clinical question/aim is important and how it extends previous work. The introduction and discussion sections are well-written. Limitations are clearly stated in the discussion. I have several comments and suggested revisions (major and minor, respectively) aimed to enhance and improve the manuscript as follows. Major comments: 1) Introduction, line 51: The authors should state what percent or proportion of T2D patients experience CKD progression or kidney failure. 2) Methods, subsection Key Outcomes, line 10: It is not clear here whether HHF is modeled separately as a distinct outcome. It is also confusing to list the HHF outcome in between a composite kidney outcome, and change in UACR/eGFR. This needs to be clarified/worded better. 3) Methods, subsection Statistical Analysis, line 49: Need to provide a reference (or references) for the stratified Cox proportional hazards models. 4) Methods, subsection Statistical Analysis, line 56: Need to specify what baseline subgroups are being referred to here. 5) Methods, subsection Statistical Analysis, line 18: Is there a rationale (and attendant reference) for why month 4 (vs say, 6 months or 1 year) was specifically chosen for chronic eGFR slope? 6) Results section: Table 1 and eTable 1 need the following: “All” column on the left for each subgroup, that displays the total N and

	%, and attendant p-values for treatment arm comparisons between finerenone vs placebo. 7) Results section: The main figures, Figure 1 and Figure 2, were hard for me to locate. They need to be fully labeled as Figure 1A, Figure 1B, etc. rather than just 1A, 1B, … as they are now. 8) Results section, subsection Efficacy (CV composite outcome by sex): The P-value for interaction on line 50 is incorrect. It should be 0.99, rather than 0.10. 9) Results section, subsection Efficacy (CV composite outcome by sex), line 52: Is there a p-value associated with the trend toward a stronger effect in older vs younger females? 10) Results section, subsection (CV composite outcome by sex): Which model was used when examining the reduction of HHF with finerenone vs placebo being more pronounced in males vs females, after adjustment for age, BMI, etc.? 11) Safety section: Again, need an “All” column on the left for Table 2 and attendant p-values for treatment arm comparisons. 12) Safety section, 3rd paragraph: Is the increased incidence of hypotension in finerenone with age, statistically significant? 13)) Safety section, 4th paragraph: The relative risk and 95% CIs of treatment discontinuation because of hyperkalemia with finerenone vs placebo is reported – but are these results reported in the tables and/or figures? Minor comments: The manuscript refers to cardiorenal outcomes, but the outcomes are modeled separately as composite cardiovascular outcomes (MACE) and composite kidney outcomes, respectively – instead of joint cardiac and kidney outcomes which would suggest assessment of bidirection association between cardiac and kidney events. The authors may consider replacing “cardiorenal” with “cardiovascular and kidney outcomes”, similar to the FIDELITY paper referenced in this work (ref 24).

REVIEWER	Parker, Victoria AstraZeneca PLC
REVIEW RETURNED	13-Oct-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript which is a post hoc subanalysis of Fidelity which in turn was a pre-specified pooled analysis of data evaluating cardiovascular outcomes from two phase 3 outcome studies (Figaro and Fidelio -DKD) undertaken in patients with DKD with and without HF. This is an interesting paper which will be of interest to the clinical community and could help support future population segmentation approaches. The authors make good justification for performing it on the basis of sex differences in steroidal metabolism and age-related differences in outcome events and the authors are transparent that this is a post hoc analysis. Comments: Abstract: See below comments, given results did not reach stat significance across all groups the conclusions need to be sharpened to reflect this. Strengths and limitations A major limitation of this study is the under-representation of women and premenopausal women in particular; the analysis was underpowered to make any meaningful inferences in this group - its covered in the discussion but should be called out as a key limitation in this section also, Results: CV composite by age: 1. The authors state CV event rates were lower in all age groups in patients treated with finerenone vs. placebo. This statement does not highlight that whilst event rates are slightly numerically lower in the < 65y group on finerenone, the CI is actually 0.81-1.10 i.e. its not significantly different vs. placebo. The same is true for the HHF analysis where the only group with a significant HR <1.0 is the age < 75 group 2. In general for the CV composite it would be nice to see a breakdown of all individual MACE components and not just HHF - e.g. what was the main driver of benefit, how did this differ across age groups CV /HHF composite by sex: 1. The authors have only looked at women subdivided by premenopausal and postmenopausal - why not have a category of female (pre and post menopausal combined also as well as the breakdowns - seems odd to omit this 2. Similar to the above claims that event rates/ CV/HHF composites are lower in finerenone treated across all groups does not reflect that some of these results (especially in women) are not stat significant and this needs to be clearly stated 3. Again seeing a breakdown of the individual MACE components would be interesting Effect of finerenone on markers of kidney function 1. The authors state that finerenone reduces chronic slope versus placebo across age and sex sub-groups. Total eGFR slope is considered the more robust measure here and there was no significant difference on total eGFR slope for any sub-analysis - this information needs to be added to this section.

	Safety Table 2 Ideally should contain a summary of the whole population AEs i.e. finerenone vs placebo for reference to the subgroups. Discussion 1) In view of the above in the results, statements in the discussion stating finerenone reduced risk of CV and kidney composite outcomes across all age groups and sex groups is not substantiated by the results, as some results did not reach statistical significance. This is apparent in the spline analyses also which show clearly that at some ages/ genders the CIs cross a hazard ratio of 1.0. This statement needs to be sharpened to make it more accurate and only include results which are stats significant. 2) Because of this opening statement, other sections need to be revised accordingly e.g. benchmarking to TOPCAT which showed age did not impact HF outcomes with spiro and saying its the same is incorrect, as there was no significant difference between finerenone and placebo on HHF in the age < 65 and 65 to 74 yr age groups 3) The authors state the elderly population had a higher risk of AEs & they occurred less freq with finerenone; yet frequencies of AEs were similar across age-groups and to placebo so this sentence seems incorrect. 4) Statement around therapeutic potential in older patients for CV/HF but not renal outcomes; this does not hold for both sexes though; the female sub analysis is underpowered and this conclusion cannot be made from this

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments:
Enthusiastically reviewed the post hoc study of the FIDELITY study, this time the authors intend to demonstrate the effect of finerenone in subgroups of patients according to their age and sex. An interesting analysis with great relevance in current nephrology, which has important merits, but also aspects that I consider can improve its quality before considering its publication.

Reviewer 1, comment 1
I suggest that in Abstract the magnitude of the decrease in CV events be added, commented by the HR obtained in each objective.
Response: Thank you for your suggestion to include the magnitude of the decrease in CV events. The abstract has been updated to include the HR obtained for the CV composite outcome for each subgroup: “Cardiovascular benefits of finerenone versus placebo were consistent across age (hazard ratio 0.94 [<65 years], 0.84 [65–74 years], 0.80 [≥75 years]; $P_{interaction}$=.42) and sex categories (hazard ratio 0.86 [male], 0.89 [premenopausal female], 0.87 [postmenopausal female]; $P_{interaction}$=.99).” Please refer to page 3 (lines 69–72) of the
revised manuscript.

Reviewer 1, comment 2

At the conclusion of the Abstract, the authors comment that finerenone is "safe", I think that phrase should not be included in this section, since the study was not designed to demonstrate safety, the title specifies CV results.
Response: As well as exploring the CV benefits of finerenone, this analysis also assessed the safety outcomes by age and sex subgroups. To clarify this in the abstract, the objectives section has been updated to: “To evaluate the efficacy and safety of finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, on cardiovascular and kidney outcomes by age and/or sex.” Please refer to page 3 (lines 55–57) of the revised manuscript. In addition, to avoid the use of the term “safe,” which may be considered vague, the abstract conclusion has been updated to: “Finerenone demonstrated a similar safety profile across age and sex subgroups.” Please see page 4 (lines 83–84) of the revised manuscript.

Reviewer 1, comment 3
In the results section, I suggest eliminating the numerator and denominator (example: 9,088/13,026), it is repetitive and necessary, just leave the percentage.
Response: As suggested, the numerators and denominators from the “Patients” section of Results have been removed to avoid repetition (page 8, lines 196–201).

Reviewer 1, comment 4
How did you identify menopausal patients? Please explain the definition in Methods.
Response: Thank you for your question. The identification of menopausal patients in this analysis was based on a comprehensive prospective cohort study (McKinlay SM, *et al. Maturitas* 1992;14:103–15) showing that the median age of onset of menopause is 51.4 years. To clarify, we have now added on page 7 (lines 165–167) of the revised manuscript: “Females were categorized as either pre- or postmenopausal if they were aged <51.4 or ≥51.4 years at baseline, respectively (based median age of menopause onset from the Massachusetts Women's Health Study).”

Reviewer 1, comment 5
Annotate the mean eGFR and median albuminuria values in the manuscript.
Response: The Results section of the manuscript has been updated to include mean eGFR and median albuminuria values across age subgroups. Please refer to page 9 (lines 205–207) of the manuscript: “Mean eGFR was 64, 54, and 48 mL/min/1.73m^2 in patients aged <65, 65–75, and ≥75 years, respectively. Median UACR was 650, 439, and 332 mg/g in patients aged <65, 65–75, and ≥75 years, respectively.”

Reviewer 1, comment 6
Add in methods section that the CONSORT guide has been followed.
Response: The following sentence referring to the FIDELIO-DKD and FIGARO-DKD trials has been added to the Methods section of the revised manuscript (page 6, lines 140–141): “These studies were reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.”

Reviewer 1, comment 7
If allowed by the Editorial group of the journal, it would be appropriate to make a Graphic Abstract that summarizes the results.
Response: Thank you for your suggestion. The journal does not currently permit the submission of a graphical abstract; therefore, we have been unable to address this comment. Please refer to Editorial comment 4: “Regarding reviewer 1’s comments (below): unfortunately we do not offer graphic abstracts as an option at this time.”

Reviewer 1, comment 8

In conclusions, I think that the positive effect that finerenone had specifically in men >75 years should be mentioned, data that I find very relevant.
Response: Thank you for your much appreciated feedback. Given that our work is a subanalysis, we feel that the data is not sufficiently powered to show significance within each age group. Additionally, no significant heterogeneity was observed for the effect of finerenone across age groups for the CV or kidney composite effects ($P_{interaction}$=0.4198 and $P_{interaction}$=0.5088, respectively). Therefore, to avoid over interpreting the data, we did not conclude that finerenone was less or more effective in one age group than another. However, our analysis did detect heterogeneity in the effect of finerenone on HHF between sex subgroups ($P_{interaction}$=0.0245), which is now highlighted in the conclusion: "In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers the risk of clinically important cardiovascular and kidney outcomes in patients with CKD and T2D across ages and sexes, with a potentially more pronounced effect on HHF in males than in females" (page 18, lines 378–381).
Reviewer 2 comments:
This work extends the results of FIDELITY to examine whether the cardiovascular and kidney benefits, as well as the safety profile of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist (MRA), are maintained across 2 key subgroups: age and sex. Age is modeled as a categorical variable. The manuscript articulates why this clinical question/aim is important and how it extends previous work. The introduction and discussion sections are well-written. Limitations are clearly stated in the discussion.
Response: We thank the reviewer for the thoughtful review and positive comments.

I have several comments and suggested revisions (major and minor, respectively) aimed to enhance and improve the manuscript as follows.

Major comments:

Reviewer 2, major comment 1
Introduction, line 51: The authors should state what percent or proportion of T2D patients experience CKD progression or kidney failure.
Response: Thank you for your suggestion to include the percentage of patients with T2D who experience CKD progression or kidney failure. The introduction has been updated to include these data: "Despite management with recommended treatments for CKD in T2D, 10–13% of patients experience CKD progression or kidney failure and are at high risk of CV events, including CV death within 2–3 years following treatment initiation." Please refer to page 5 (lines 119–121) of the revised manuscript.

Reviewer 2, major comment 2
Methods, subsection Key Outcomes, line 10: It is not clear here whether HHF is modelled separately as a distinct outcome. It is also confusing to list the HHF outcome in between a composite kidney outcome, and change in UACR/eGFR. This needs to be clarified/worded better.
Response: Thank you for your feedback. The Key Outcomes section of the Methods has now been updated to provide additional clarity. Please refer to page 7 (lines 154–157) of the revised manuscript: "Efficacy outcomes included a CV composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF (HHF), and a kidney composite outcome of kidney failure, sustained ≥57% eGFR decline, or renal death. Additional outcomes included HHF and change in UACR and eGFR over time."

Reviewer 2, major comment 3
Methods, subsection Statistical Analysis, line 49: Need to provide a reference (or references) for the stratified Cox proportional hazards models.
Response: References explaining the stratified Cox proportional hazards model and its use in analyses of multicenter trial data (Kleinbaum DG & Klein M. Survival analysis: A self-learning text.

New York, NY: Springer New York 2012:201–40 and Therneau TM & Grambsch PM. Modeling survival data: Extending the Cox model. New York, NY: Springer New York 2000:39–77) have been added as requested; please refer to page 7 (line 175).

Reviewer 2, major comment 4
Methods, subsection Statistical Analysis, line 56: Need to specify what baseline subgroups are being referred to here.
Response: Thank you for your comment. The "Statistical Analysis" section of Methods has been updated to clarify baseline subgroups: "The *P*-values for interaction between the treatment group (finerenone or placebo) and each baseline subgroup (age or sex) were based on stratified Cox proportional hazards models, accounting for the treatment effect, the subgroup effect, and their interaction." Please refer to page 8 (lines 177–180) of the revised manuscript.

Reviewer 2, major comment 5
Methods, subsection Statistical Analysis, line 18: Is there a rationale (and attendant reference) for why month 4 (vs say, 6 months or 1 year) was specifically chosen for chronic eGFR slope?
Response: Thank you for your question regarding the rationale for the chronic eGFR slope timepoints. For the FIDELIO-DKD and FIGARO-DKD trials, patients were scheduled to visit the clinics during randomization, month 1, month 4, and every 4 months thereafter until end of study, during which eGFR samples were collected. In both trials, an initial eGFR decline was noted during month 1 of follow-up (Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–29 [supplementary appendix] and Ruilope LM, *et al. Nephrol Dial Transplant* 2023;38:372–83 [supplementary material]), which we defined as an acute eGFR slope; a common observation that has also been reported for RASis and SGLT-2is (Oshima M, *et al. Kidney Int* 2021;99:999–1009; Holtkamp FA, *et al. Kidney Int* 2011;80:282–87; Kraus BJ, *et al. Kidney Int* 2021;99:750–62). In a population pharmacokinetics and pharmacodynamics analysis using data from the phase IIb studies, ARTS-DN (NCT01874431) and ARTS-DN Japan (NCT01968668), it was reported that the pharmacokinetic model-predicted time for the effect of finerenone on eGFR to reach a steady-state was 85 days from treatment initiation (Snelder N, *et al. Clin Pharmacokinet* 2020;59:359–70). Therefore, month 4 was the first study visit at which the eGFR slope would be considered to have transitioned from the acute to the chronic stage, and thus, the selected timepoint to initiate the chronic eGFR slope in the current analysis.

Reviewer 2, major comment 6
Results section: Table 1 and eTable 1 need the following: "All" column on the left for each subgroup, that displays the total N and %, and attendant p-values for treatment arm comparisons between finerenone vs placebo.
Response: Table 1 and eTable 1 (page 10 of the revised manuscript and page 2 of the revised supplement, respectively) have been revised to include "All" columns on the left displaying total *N* and % values as suggested. However, we did not include *P*-values for treatment arm comparisons between finerenone and placebo for the baseline characteristics because these data were presented to show a representation of the sample and not intended as part of the main hypothesis of this analysis. In addition, patients were randomized 1:1 to finerenone or placebo during the FIDELIO-DKD and FIGARO-DKD trials; therefore, the presented data were from two balanced groups.

Reviewer 2, major comment 7
Results section: The main figures, Figure 1 and Figure 2, were hard for me to locate. They need to be fully labeled as Figure 1A, Figure 1B, etc. rather than just 1A, 1B, … as they are now.
Response: Thank you for your feedback. The Results section of the revised manuscript has been updated to fully label figures, for example: "eFigure 2B, eFigure 2C."

Reviewer 2, major comment 8
Results section, subsection Efficacy (CV composite outcome by sex): The P-value for interaction on line 50 is incorrect. It should be 0.99, rather than 0.10.
Response: Thank you for bringing this point to our attention. The *P*-value for interaction for the CV composite outcome across sex subgroups has now been corrected to 0.99. Please see page 14 (line 234) of the revised manuscript.

Reviewer 2, major comment 9
Results section, subsection Efficacy (CV composite outcome by sex), line 52: Is there a p-value associated with the trend toward a stronger effect in older vs younger females?
Response: Thank you for this question. eFigure 2C, where this trend was noted, has been revised to include *P*-values (see page 11 of the revised supplement). However, given that the cubic splines for hazard ratio of the CV composite outcome were used to model the effect of finerenone vs placebo with increasing age by male and female subgroups (i.e. analyzed as a continuous variable), no specific *P*-value is available for the older vs younger female patients in eFigure 2C. Nevertheless, it can be seen in eFigure 2C that female patients aged approximately <65 years had hazard ratios >1 (favoring placebo), while those aged >65 years had hazard ratios <1. This trend in hazard ratio appeared to consistently decrease with increasing age.

Reviewer 2, major comment 10
Results section, subsection (CV composite outcome by sex): Which model was used when examining the reduction of HHF with finerenone vs placebo being more pronounced in males vs females, after adjustment for age, BMI, etc.?
Response: Thank you for your comment. These data were based on stratified Cox proportional hazards models, as outlined in the "Statistical Analysis" subsection of Methods: "Stratified Cox proportional hazards models, including stratification factors: geographic region, eGFR and albuminuria category at screening, history of CV disease, and study, were used for the analysis of time-to-event clinical outcomes with stratification factors: geographic region, eGFR and albuminuria category at screening, history of CV disease, and study. The *P*-values for interaction between the treatment group (finerenone or placebo) and each baseline subgroup (age or sex) were based on stratified Cox proportional hazards models, accounting for the treatment effect, the subgroup effect, and their interaction." Please refer to page 7 and 8 (lines 175–180) of the revised manuscript.

Reviewer 2, major comment 11
Safety section: Again, need an "All" column on the left for Table 2 and attendant p-values for treatment arm comparisons.
Response: Thank you for this suggestion. "All" columns for the overall finerenone and placebo groups have been added to the revised eTable 2 (moved to the supplement file; see page 6) as suggested. However, given the relatively small number of AEs per subgroup and consequent limited ability to make proper statistical inference, the statistical significance of safety outcomes was not assessed neither in this analysis nor in the overall FIDELITY analysis, where these values (overall safety outcomes for finerenone and placebo) were previously reported (Agarwal R, *et al. Eur Heart J*. 2022;43:474–84).

Reviewer 2, major comment 12
Safety section, 3rd paragraph: Is the increased incidence of hypotension in finerenone with age, statistically significant?
Response: Thank you for this question. As briefly mentioned in the response to the previous comment, formal hypothesis tests of safety outcomes including the incidence of hypotension by age were not performed in this study given that the number of AEs per subgroup was relatively small to make proper statistical inference. Instead, we describe the observed trend. The language used in the Results text describing the incidence of hypotension has been adjusted to acknowledge that the

reported effect is based on an observed trend, not a statistically significant difference: "A trend of increased incidence of hypotension with increasing age was observed in patients treated with finerenone; however, the incidence of hypotension was generally low across all age subgroups (<6%; eTable 2)" (page 14, lines 283–285).

Reviewer 2, major comment 13

Safety section, 4th paragraph: The relative risk and 95% CIs of treatment discontinuation because of hyperkalemia with finerenone vs placebo is reported – but are these results reported in the tables and/or figures?

Response: Data on the relative risk of treatment discontinuation due to hyperkalemia by age and sex subgroups have now been included the supplementary materials. Please refer to page 15 of the revised supplement (eFigure 6).

Minor comments:

Reviewer 2, minor comment 1

The manuscript refers to cardiorenal outcomes, but the outcomes are modeled separately as composite cardiovascular outcomes (MACE) and composite kidney outcomes, respectively – instead of joint cardiac and kidney outcomes which would suggest assessment of bidirection association between cardiac and kidney events. The authors may consider replacing “cardiorenal” with “cardiovascular and kidney outcomes”, similar to the FIDELITY paper referenced in this work (ref 24).

Response: Thank you for your suggestion to replace “cardiorenal” with “cardiovascular and kidney outcomes” to align with the FIDELITY manuscript. This update has been made throughout the revised manuscript.

Reviewer 3 comments:

Thank you for the opportunity to review this manuscript which is a post hoc subanalysis of Fidelity which in turn was a pre-specified pooled analysis of data evaluating cardiovascular outcomes from two phase 3 outcome studies (Figaro and Fidelio -DKD) undertaken in patients with DKD with and without HF. This is an interesting paper which will be of interest to the clinical community and could help support future population segmentation approaches. The authors make good justification for performing it on the basis of sex differences in steroidal metabolism and age-related differences in outcome events and the authors are transparent that this is a post hoc analysis.

Response: We thank the reviewer for highlighting these salient points.

Comments:

Reviewer 3, comment 1 (Abstract)

See below comments, given results did not reach stat significance across all groups the conclusions need to be sharpened to reflect this.

Response: Thank you for your comment. The Abstract conclusion has now been updated to reflect the fact that no significant heterogeneity was observed between age and sex subgroups for the cardiovascular or kidney composite outcomes. We also highlighted that significant heterogeneity was detected in the analysis of the effect of finerenone on hospitalization for heart failure, with a more pronounced effect observed in males compared with females. Please see page 4 (lines 81–83) of the revised manuscript: “Finerenone improved cardiovascular and kidney composite outcomes with no significant heterogeneity between age and sex subgroups; however, the effect on hospitalization for heart failure appeared more pronounced in males.”

Reviewer 3, comment 2 (Strengths and limitations)

A major limitation of this study is the under-representation of women and premenopausal women in particular; the analysis was underpowered to make any meaningful inferences in this group - its covered in the discussion but should be called out as a key limitation in this section also,

Response: Thank you for your suggestion to include the under-representation of women as a major limitation of the study. The limitations section of the Discussion has been updated to include

the following: “Sample size and number of events for females, particularly premenopausal females, were small. Therefore, there is uncertainty around the estimates and the analysis was underpowered to draw meaningful conclusions in this subgroup.” Please see page 17 (lines 364–366) of the revised manuscrit.

Reviewer 3, comment 3 (Results, CV composite by age)
1. The authors state CV event rates were lower in all age groups in patients treated with finerenone vs. placebo. This statement does not highlight that whilst event rates are slightly numerically lower in the < 65y group on finerenone, the CI is actually 0.81-1.10 i.e. its not significantly different vs. placebo. The same is true for the HHF analysis where the only group with a significant HR <1.0 is the age < 75 group
Response: Thank you for highlighting this point. For accuracy, the text has been revised as follows: “Treatment with finerenone resulted in a numerical reduction in CV composite event rates versus placebo in all age groups (Figure 1A); however, no significant heterogeneity was observed for the effect of finerenone across categorical age subgroups ($P_{interaction}$=.42)” (Page 12, lines 219–222). Similar amends were made to the HHF analysis Results text. Please see page 12 (lines 227–229)

Reviewer 3, comment 4 (Results, CV composite by age)
In general for the CV composite it would be nice to see a breakdown of all individual MACE components and not just HHF - e.g. what was the main driver of benefit, how did this differ across age groups
Response: As suggested, forest plots including the subcomponents of the CV composite outcome have been added to the supplement (eFigure 1; revised supplement, page 8) and cited in the Results section. Please see page 12 (lines 219, 232 and 241)

Reviewer 3, comment 5 (Results, CV composite by sex)
The authors have only looked at women subdivided by premenopausal and postmenopausal - why not have a category of female (pre and post menopausal combined also as well as the breakdowns - seems odd to omit this
Response: Thank you for your feedback on this point. The rationale behind splitting the female population by premenopause and postmenopause is based on extensive research showing that CV risk becomes more pronounced in women following menopause. For example, young females are protected from CV disease vs age-matched males, whereas CV disease development occurs more rapidly in females after menopause such that the risk eventually equals or exceeds that of age-matched males (DuPont JJ, *et al. Am J Physiol Heart Circ Physiol* 2021;320:169–80). We feel that these data would be informative and valuable to the scientific community.

Reviewer 3, comment 6 (Results, CV composite by sex)
Similar to the above claims that event rates/ CV/HHF composites are lower in finerenone treated across all groups does not reflect that some of these results (especially in women) are not stat significant and this needs to be clearly stated
Response: As above, the results text has been revised to note that CV composite event rates were numerically lower with finerenone vs placebo across the sex subgroups. Please see page 12 (line 231). For data on HHF, the results indicate significant heterogeneity observed between the sex subgroups, suggesting that the beneficial effect of finerenone on this outcome was more pronounced in males (page 12, lines 241 and page 13, lines 242–243). This finding is also highlighted in the Discussion page 21 (lines 349–352). Additionally, we have now added: “however, the effect on hospitalization for heart failure appeared more pronounced in males” to the Abstract conclusion (page 4, lines 82–83). to further emphasize this point in the manuscript.

Reviewer 3, comment 7 (Results, CV composite by sex)

Again seeing a breakdown of the individual MACE components would be interesting
Response: Components of the CV composite outcome by age and sex have been included in the updated supplement (eFigure 1). Please see our response to comment 4 you provided for additional details.

Reviewer 3, comment 8 (Results, Effect of finerenone on markers of kidney function)
1. The authors state that finerenone reduces chronic slope versus placebo across age and sex sub-groups. Total eGFR slope is considered the more robust measure here and there was no significant difference on total eGFR slope for any sub-analysis - this information needs to be added to this section.
Response: Thank you for your comment. We have only reported the chronic eGFR slope because we believe it is more representative of the treatment benefit of finerenone versus placebo after the transient phase (early acute eGFR drop) has passed. The chronic slope estimates the rate of change in eGFR once the stationary phase is reached, which is of clinical interest for long term clinical outcomes. The total slope, on the other hand, includes the acute phase in the calculation, and as shown in Figure 3 and eFigure 4, the average trajectory of the population cannot be captured or well described with a single linear curve for subjects treated with finerenone. Instead, a better fit to the observed data is obtained by partitioning the trajectory into two sections, the acute and chronic phases. Therefore, we believe that the inclusion of the total eGFR slope could potentially be misleading if compared directly with the chronic eGFR slope.

Reviewer 3, comment 9 (Results, Safety)
Table 2 ideally should contain a summary of the whole population AEs i.e. finerenone vs placebo for reference to the subgroups.
Response: Thank you for the suggestion. Two additional columns (finerenone and placebo) have now been added to the revised eTable 2 (moved to the supplement file; see page 6) to show a summary of AEs in the overall FIDELITY population. For additional details, please refer to our response to Reviewer 2, major comment 11.
Reviewer 3, comment 10 (Discussion)
In view of the above in the results, statements in the discussion stating finerenone reduced risk of CV and kidney composite outcomes across all age groups and sex groups is not substantiated by the results, as some results did not reach statistical significance. This is apparent in the spline analyses also which show clearly that at some ages/ genders the CIs cross a hazard ratio of 1.0. This statement needs to be sharpened to make it more accurate and only include results which are stats significant.
Response: Thank you for your comments. In line with your previous comments, the Results section has been amended to clearly state that finerenone reduced the risk of the CV and kidney composite outcomes without significant heterogeneity observed across age and sex subgroups (i.e. based on the nonsignificant *P*-value for interaction), except for hospitalization for heart failure, for which the beneficial effect of finerenone appeared to be more pronounced in the male subgroup compared with the two female subgroups ($P_{interaction}$=.02). Based on the present results, it would not be statistically accurate to conclude that finerenone was less effective in one age group than another. Nevertheless, the language used in the first statement of the discussion has been softened to take into consideration some of the potential differences observed between subgroups that were not supported by the *P*-values for interaction reported in this manuscript (page 19, line 300). Furthermore, it is worth noting that the premenopausal female subgroup had a very small sample size (*n*=323), thus, the analysis was underpowered to draw definitive conclusions on differences observed between sex subgroups. This point has been acknowledged and included as a limitation in the revised Discussion (page 17, lines 352–354 and page 17, lines 364–366).

Reviewer 3, comment 11 (Discussion)

Because of this opening statement, other sections need to be revised accordingly e.g. benchmarking to TOPCAT which showed age did not impact HF outcomes with spiro and saying its the same is incorrect, as there was no significant difference between finerenone and placebo on HHF in the age < 65 and 65 to 74 yr age groups

Response: Thank you for your comment. As mentioned in our response to your previous comment, as this is a subanalysis, the study was not powered to draw conclusions for individual age groups due to low patient numbers in the subgroups. For this reason, there are wide CIs in those age subgroups, and consequently p-values have not been included for subgroups. Therefore, any inferences made in the discussion and comparison to studies such as TOPCAT relate to whether any treatment modification was shown across age subgroups, based on the p-value for interaction. To address your comment, the language used to link the studies has been amended in the revised manuscript and key differenceincluding patient populations and key outcomes have been made clearer (page 15, lines 311–312 and 312–316)**.**

Reviewer 3, comment 12 (Discussion)

The authors state the elderly population had a higher risk of AEs & they occurred less freq with finerenone; yet frequencies of AEs were similar across age-groups and to placebo so this sentence seems incorrect.

Response: Thank you for flagging this point. We have now corrected the Discussion statements to: "In this study, the elderly population had higher risk of certain AEs including hypotension, AEs leading to discontinuation, and death. Hypotension occurred more frequently in the finerenone group but did not seem to substantially affect related clinical outcomes" (page 16, lines 327–329).

Reviewer 3, comment 13 (Discussion)

Statement around therapeutic potential in older patients for CV/HF but not renal outcomes; this does not hold for both sexes though; the female sub analysis is underpowered and this conclusion cannot be made from this

Response: Thank you for your feedback. As per your comment, the study was underpowered to derive definitive conclusions regarding the effect of finerenone on CV and kidney outcomes in female patients as well as kidney outcomes in patients aged ≥75 years. The statement mentioned has, therefore, been moved from the conclusion to the main body of the Discussion and reworded accordingly (page 16, lines 3–348 and page 17, lines 349–354). Additionally, we have included the sample size and low number of events in the female subgroup as a limitation (page 17, lines 364–366).

VERSION 2 – REVIEW

REVIEWER	Chávez-Iñiguez, Jonathan University of Guadalajara, Nephrology
REVIEW RETURNED	09-Jan-2024

GENERAL COMMENTS	I appreciate the effort that the authors have made to satisfy my questions and requests, I congratulate them for this important work.

REVIEWER	Ghosh, Alokananda The George Washington University Biostatistics Center, Biostatistics and Bioinformatics
REVIEW RETURNED	26-Jan-2024

GENERAL COMMENTS	I appreciate the authors' incorporation of my feedback and I believe that they have adequately addressed my queries/critiques.

REVIEWER	Parker, Victoria AstraZeneca PLC
REVIEW RETURNED	09-Jan-2024

GENERAL COMMENTS	Thank you to the authors for making revisions. The manuscript reads well. Minor revision: In the abstract, hazard ratios are presented, however the 95% CIs are not presented and therefore, it is a bit misleading as it does not convey that many of these result did not reach stat significance (likely owing to be underpowered) but all the same, if there is word count space, adding 95% CIs would help here or otherwise capturing somehow that these did not reach stats significance.