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ORIGINAL ARTICLE

Finerenone and effects on mortality in chronic kidney disease and type 2 diabetes: a FIDELITY analysis

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Aims Finerenone reduces the risk of cardiovascular events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). We investigated the causes of mortality in the FIDELITY population.

Methods and results The FIDELITY prespecified pooled data analysis from FIDELIO-DKD and FIGARO-DKD excluded patients with heart failure and reduced ejection fraction. Outcomes included intention-to-treat and prespecified on-treatment analyses of the risk of all-cause and cardiovascular mortality. Of 13 026 patients [mean age, 64.8 years; mean estimated glomerular filtration rate (eGFR), 57.6 mL/min/1.73 m^2], 99.8% were on renin–angiotensin system inhibitors. Finerenone reduced the incidence of all-cause and cardiovascular mortality vs. placebo (8.5% vs. 9.4% and 4.9% vs. 5.6%, respectively) and demonstrated significant on-treatment reductions [hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.70–0.96; $P = 0.014$ and HR, 0.82; 95% CI, 0.67–0.99; $P = 0.040$, respectively]. Cardiovascular-related mortality was most common, and finerenone lowered the incidence of sudden cardiac death vs. placebo [1.3% (incidence rate 0.44/100 patient-years) vs. 1.8% (0.58/100 patient-years), respectively; HR, 0.75; 95% CI, 0.57–0.996; $P = 0.046$]. The effects of finerenone on mortality were similar across all Kidney Disease: Improving Global Outcomes risk groups. Event probability with finerenone at 4 years was consistent irrespective of baseline urine albumin-to-creatinine ratio, but seemingly more pronounced in patients with higher baseline eGFR.

Conclusion In FIDELITY, finerenone significantly reduced the risk of all-cause and cardiovascular mortality vs. placebo in patients with T2D across a broad spectrum of CKD stages while on treatment, as well as sudden cardiac death in the intention-to-treat population.

Clinical trials registration FIDELIO-DKD and FIGARO-DKD are registered with ClinicalTrials.gov, numbers NCT02540993 and NCT02545049, respectively (funded by Bayer AG).

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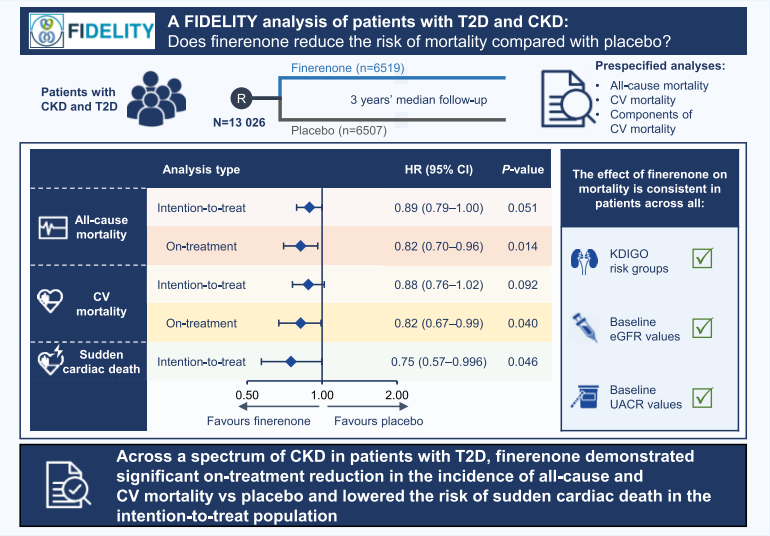
Graphical Abstract



Finerenone demonstrated significant on-treatment reduction in the incidence of all-cause and cardiovascular mortality in patients with chronic kidney disease and type 2 diabetes. Sudden cardiac death was also lowered when the intention-to-treat population was assessed. These effects with finerenone were consistent across Kidney Disease: Improving Global Outcomes risk groups, irrespective of baseline urine albumin-to-creatinine ratio, but were more pronounced in patients with higher baseline estimated glomerular filtration rate.

Keywords Chronic kidney disease • Type 2 diabetes • All-cause mortality • Cardiovascular mortality • Finerenone • Non-steroidal MRA

Introduction

With the rising global burden of chronic kidney disease (CKD) and type 2 diabetes (T2D),[1] the increased incidence of mortality associated with these comorbidities remains a societal cause for concern.[2] The global age-standardized mortality rate for CKD due to diabetes increased by ∼107% between 1990 and 2013,[3] and life expectancy of patients with T2D and early CKD was reduced by up to 16 years.[4] Predominant causes of mortality in patients with CKD and T2D are cardiovascular (CV) events, with an observed six-fold higher risk vs. the general population,[2,5] and sudden cardiac death reported as a frequent cause of CV mortality.[5] Impaired estimated glomerular filtration rate (eGFR) and the presence of albuminuria increase the risk of all-cause and CV mortality in this patient population, highlighting the importance of preserving kidney function.[2] Other causes, such as infection and malignancy, may also contribute to mortality in patients with CKD and diabetes.[6,7]

Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) have been shown to reduce the risk of CKD progression and are recommended for the treatment of patients with hypertension, CKD, and T2D.[8] However, despite their kidney protective benefits, these therapeutic agents were not reported to reduce the risk of all-cause mortality in this population.[9] Mineralocorticoid receptor antagonists (MRAs) can be effective in a range of disorders, including CKD, but the use of steroidal MRAs is limited by off-target side effects, such as hyperkalaemia, and sexual side effects, including breast pain and gynaecomastia.[10] Finerenone is a distinct, selective, non-steroidal MRA that offers cardiorenal protection in patients with CKD and T2D, with a low risk of hyperkalaemia and no sexual side effects.[11–13] These benefits with finerenone, demonstrated in two complementary Phase III trials on top of treatment with an optimized dose of an ACEi or an ARB [FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD), NCT02540993; and FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD), NCT02545049], appear largely independent of metabolic factors, with a small proportion of the clinical effect attributed to a modest reduction in blood pressure (BP) as demonstrated in a subanalysis of the FIDELIO-DKD trial.[14,15] A pooled analysis of these trials, including>13 000 patients with CKD and T2D [FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis (FIDELITY)], has been performed and has provided robust evidence of the CV and kidney benefits of finerenone.[16] In this FIDELITY analysis, we present findings regarding the causes of mortality in patients with T2D across a broad spectrum of CKD stages who were treated with finerenone or placebo.

Methods

Study design and participants

FIDELITY was a prespecified, exploratory pooled analysis of individual patient data from two Phase III studies, FIDELIO-DKD and FIGARO-DKD, with all-cause mortality as a prespecified secondary endpoint in the individual studies and an efficacy outcome of interest in the pooled analysis.[16] FIDELIO-DKD and FIGARO-DKD were international, randomized, double-blind, placebo-controlled, multicentre trials with complementary outcomes. The design, baseline characteristics, eligibility criteria, and primary results of the two studies have been published previously.[11,12] In brief, all participants provided written informed consent, and the studies were performed in accordance with the principles of the

Declaration of Helsinki and approved by an ethics committee at each investigative site.[11,12] Adult patients with T2D and CKD [eGFR ≥ 25 to ≤90 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio (UACR) ≥ 30 to <300 mg/g or eGFR ≥ 25 mL/min/1.73 m^2 and UACR ≥ 300 to ≤5000 mg/g) were enrolled. Maximal tolerated labelled dose of an ACEi or ARB for ≥4 weeks before screening was required. Key exclusion criteria were as follows: (i) heart failure (HF) with reduced ejection fraction and New York Heart Association Classes II–IV (Class 1A recommendation for MRAs); (ii) known significant non-diabetic kidney disease; (iii) incidence of stroke, transient ischaemic cerebral attack, acute coronary syndrome, or hospitalization for worsening HF, ≤30 days prior to the screening visit; (iv) dialysis for acute renal failure within 12 weeks prior to the run-in visit; and (v) any other condition that would make the patient unsuitable for the study and would not allow participation for the full planned study period.

Outcomes

All fatal events were adjudicated prospectively by an independent clinical event committee blinded to treatment allocation. Outcomes assessed in this analysis included all-cause mortality, CV mortality (Supplementary Methods),[11,12] renal mortality, and non-CV, non-renal mortality. An on-treatment analysis for all-cause mortality and CV mortality outcomes was also performed, which included events that occurred while on treatment and for up to 30 days after the last intake of study medication. Events were classified as non-CV, non-renal mortality if mortality was not thought to be due to a CV or renal cause. Non-CV, non-renal mortalities were categorized as infection, malignancy, or other specific causes.

Specific causes of mortality were assessed in the overall patient population and according to the Kidney Disease: Improving Global Outcomes (KDIGO) risk group classification, where the risk of CKD progression is classified using specific eGFR and albuminuria categories that were ranked based on relative risk in a meta-analysis of 45 cohorts that included >1.5 million participants.[17] The current heat map for CKD prognosis according to KDIGO is shown in Supplementary material online, *Figure 1* and classifies patients into four categories: low, moderate, high, and very high risk of CKD progression.[8] Event probability analyses at 4 years were also performed for time to all-cause mortality, CV mortality, and sudden cardiac death by baseline eGFR and UACR (both dealt as continuous variables) and by serum potassium values at month 4 (for events that occurred after month 4).

Statistics

Outcomes were analysed in the pooled full analysis set (by planned treatment) as described previously.[16] Time to all-cause mortality was a prespecified analysis. Exploratory analyses included time to CV mortality and time to non-CV, non-renal death. Analysis included descriptive statistics and a statistical test for interaction, subject to sufficient sample size for each subgroup. Incidence rates [*n* per 100 patient-years (PY)] were calculated for mortality events from randomization up to the end-of-study visit, and patients without an event were censored at the date of their last contact with complete information on all components of the respective outcome (defined as primary analysis). A prespecified on-treatment analysis was also performed and was restricted to the time frame of the primary analysis to 30 days after the last study drug intake. Incidence rates were estimated based on the number of patients, with incident events divided by the cumulative at-risk time in the reference population, where a patient is no longer at risk once an incident event occurred. Exact Poisson confidence intervals (CIs) were also calculated.

Treatment effects, expressed as hazard ratios (HRs) with corresponding 95% CIs, were derived from a stratified Cox proportional hazards model fitted with stratification factors study, history of CV disease, region, eGFR category at screening, and type of albuminuria at screening. Interaction *P* values display the study × treatment interaction based on a stratified model, including study, treatment, and study × treatment as covariates. The *P*-value is based on a two-sided stratified log-rank test. Event probability at 4 years was based on Cox regressions adjusted for covariates treatment, study, history of CV disease, region, race, sex, age, glycated haemoglobin (HbA1c), systolic BP (SBP), eGFR, and UACR at baseline and was assessed by baseline eGFR, baseline UACR, or serum potassium values at month 4 as a continuous variable.

Risk factors for sudden cardiac death were identified using a Cox regression model stratified by study with stepwise variable selection using a predefined list of variables based on medical judgement (Supplementary material online, *Table 1*). Significance level 0.1 was used for entry and 0.05 was used for variables to stay in the model.

Results

Patients

A total of 13 026 patients were included in the analysis (finerenone; $n = 6519$ and placebo; $n = 6507$). The mean age was 64.8 years, and 69.8% of patients were male. At baseline, patients had a mean eGFR of 57.6 mL/min/1.73 m^2, median UACR of 515 mg/g, mean SBP of 136.7 mmHg, and mean HbA1c of 7.7%. The mean duration of diabetes was 15.4 years, and 45.6% of patients had a history of atherosclerotic CV disease (ASCVD) at baseline. Most patients were taking an ACEi or an ARB (99.8%), 51.5% were receiving a diuretic, 72.2% were taking statins, and 49.9% were on beta-blockers at baseline. Most patients (97.7%) were receiving at least one glucose-lowering therapy at baseline, with 58.6% patients taking insulin, 7.2% receiving a glucagon-like peptide-1 receptor agonist, and 6.7% receiving a sodium-glucose co-transporter-2 inhibitor (SGLT-2i) (Supplementary material online, *Table 2*).

Overall mortality incidence rates

In the overall FIDELITY population, the incidence of all-cause mortality occurred in 552 patients with finerenone (8.5%; *n* per 100 PY, 2.76) vs. 614 patients with placebo (9.4%; *n* per 100 PY, 3.10; HR, 0.89; 95% CI, 0.79–1.00; $P = 0.051$), and the incidence of CV mortality occurred in 322 patients with finerenone (4.9%; *n* per 100 PY, 1.61) vs. 364 patients with placebo (5.6%; *n* per 100 PY, 1.84; HR, 0.88; 95% CI, 0.76–1.02; $P = 0.092$; *Figure 1*). An on-treatment analysis revealed that all-cause mortality and CV mortality were significantly lower with finerenone vs. placebo. The incidence of all-cause mortality occurred in 280 patients with finerenone (4.3%; *n* per 100 PY, 1.62) vs. 344 patients with placebo (5.3%; *n* per 100 PY, 1.98; HR, 0.82, 95% CI, 0.70–0.96, $P = 0.014$), and the incidence of CV mortality occurred in 189 patients with finerenone (2.9%; *n* per 100 PY, 1.09) vs. 233 patients with placebo (3.6%; *n* per 100 PY, 1.34; HR, 0.82; 95% CI, 0.67–0.99; $P = 0.040$; *Figure 1*).

Causes of mortality in the total population

In the overall FIDELITY population, the most common cause of mortality was CV-related in both the finerenone and placebo groups [322 (4.9%) vs. 364 (5.6%) patients with events, respectively; *Figure 2* and Supplementary material online, *Figure 2*], with undetermined CV mortality and sudden cardiac death occurring at the highest frequency [143 (2.2%) patients with finerenone vs. 153 (2.4%) patients with placebo and 88 (1.3%) patients with finerenone vs. 115 (1.8%) patients with placebo, respectively].

Undetermined CV mortality, sudden cardiac death, and mortality from stroke and HF appeared to be lower with finerenone vs. placebo. Significance was reached for the incidence of sudden cardiac death with finerenone vs. placebo, which occurred in 88 patients with finerenone (1.3%, *n* per 100 PY, 0.44) and 115 patients with placebo (1.8%, *n* per 100 PY, 0.58; HR, 0.75; 0.57–0.996; $P = 0.046$;

Endpoint	Finerenone (n=6519)		Placebo (n=6507)		Hazard ratio (95% CI)	P-value
	n (%)	n/100 PY	n (%)	n/100 PY		
Primary analysis						
All-cause mortality	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–1.00)	0.051
CV mortality	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
On-treatment analysis[a]						
All-cause mortality	280 (4.3)	1.62	344 (5.3)	1.98	0.82 (0.70–0.96)	0.014
CV mortality	189 (2.9)	1.09	233 (3.6)	1.34	0.82 (0.67–0.99)	0.040

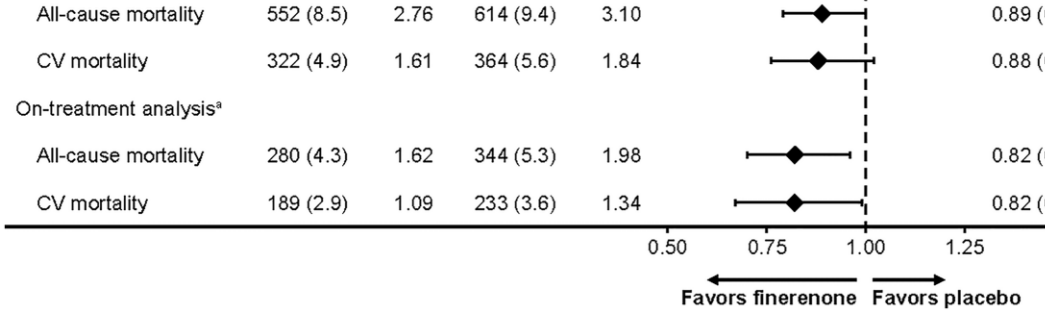


Figure 1 Risk of all-cause mortality and CV mortality (primary intention-to-treat analysis and on-treatment analysis). [a]Time frame of the on-treatment analysis was restricted to 30 days after the last study drug intake. CI, confidence interval; CV, cardiovascular; and PY, patient-years.

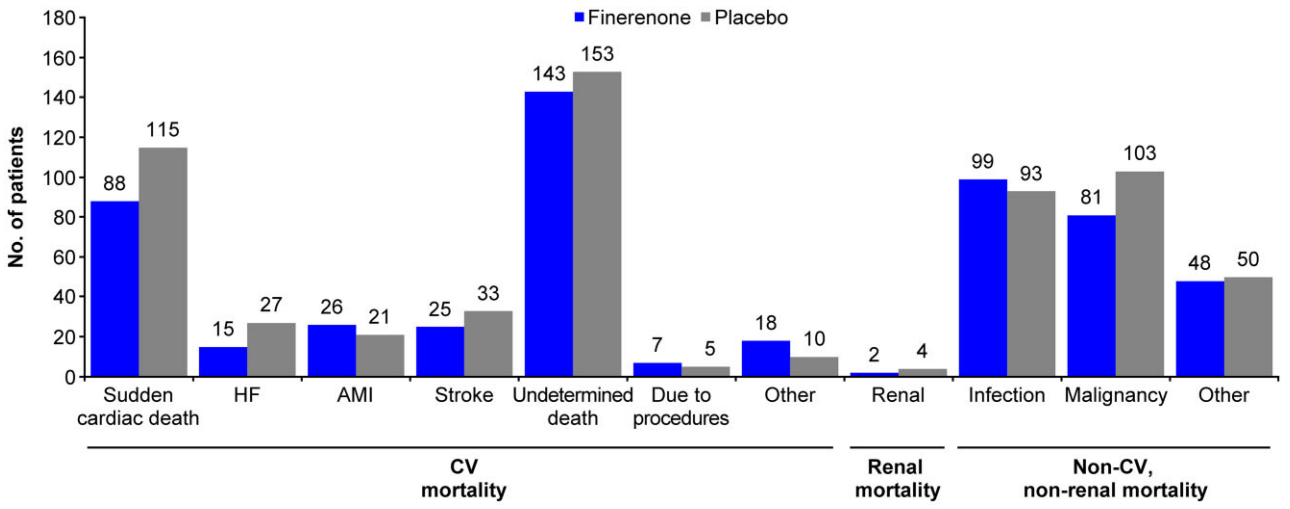


Figure 2 Causes of mortality following treatment with finerenone and placebo. AMI, acute myocardial infarction; CV, cardiovascular; and HF, heart failure.

Supplementary material online, *Figure 2*). Multivariate analyses using a stepwise variable selection identified region, treatment with finerenone, eGFR at baseline, UACR at baseline, HbA1c at baseline, high-sensitivity C-reactive protein at baseline, history of coronary artery disease, history of ischaemic stroke, history of atrial fibrillation and atrial flutter, history of HF, and age at baseline as factors influencing the occurrence of sudden cardiac death (Supplementary material online, *Table 3*).

The incidence of non-CV and non-renal mortality, including mortality from malignancy, infection, and other causes, occurred in 228 patients (3.5%) with finerenone and 246 patients (3.8%) with placebo. The incidence of mortality due to malignancy occurred in 1.2% patients with finerenone vs. 1.6% patients with placebo (HR, 0.79; 0.59–1.05). The incidence of renal mortality was low in the overall FIDELITY population (<0.1% in both treatment arms; *Figure 2* and Supplementary material online, *Figure 2*).

Causes of mortality in patient subpopulations

To investigate whether the effect of finerenone was consistent irrespective of CKD severity, the FIDELITY population was grouped according to the KDIGO risk classification of CKD progression.[8] Patients in FIDELITY were classified as low (n = 64), moderate (n = 1323), high (n = 5345), and very high (n = 6288) risk of CKD progression. A total of six patients could not be assigned to a KDIGO risk category for CKD progression due to missing data for eGFR and/or UACR at baseline. Most baseline characteristics were similar among the KDIGO risk groups (Supplementary material online, *Table 2*), with differences observed in the mean duration of diabetes, baseline use of insulin, potassium binders, and mean high-sensitivity C-reactive protein levels, which increased with higher KDIGO risk group classification. There were more patients with a medical history

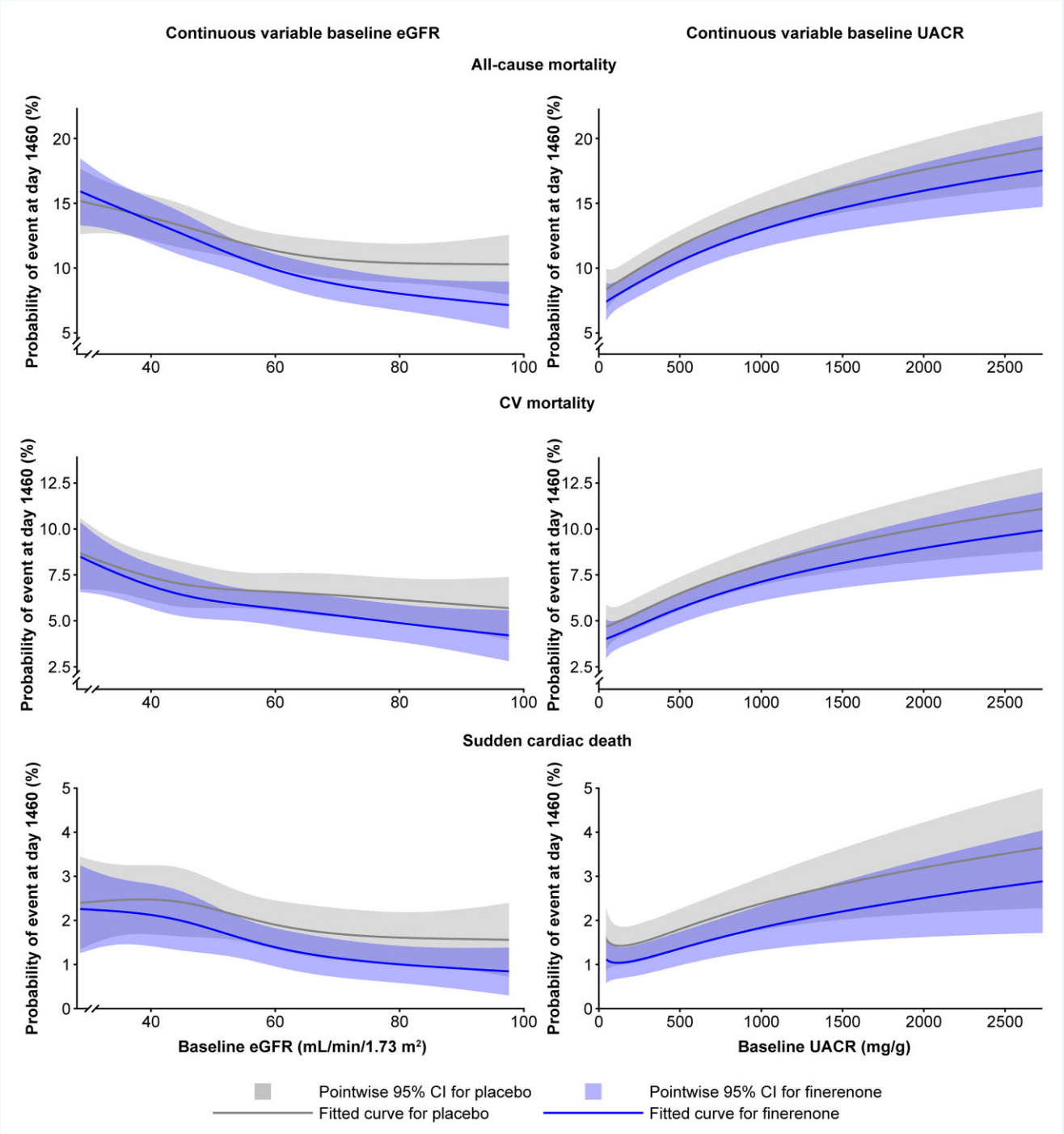


Figure 3 Event probability of time to all-cause mortality, CV mortality, or sudden cardiac death at 4 years according to continuous variable baseline eGFR or baseline UACR in the intention-to-treat population. Event probability was analysed according to continuous variable baseline eGFR or UACR. Cox proportional hazards model was fitted with covariates baseline eGFR (for continuous variable baseline eGFR) or baseline UACR (log-transformed; for continuous variable baseline UACR), treatment, study, ASCVD history, region, sex, race, and continuous covariates age, HbA1c, SBP, baseline UACR (log-transformed; for continuous variable baseline eGFR) or baseline eGFR (for continuous variable baseline UACR). Splines were used with knots at eGFR 30, 45, 60, and 90 mL/min/1.73 m^2 (for continuous variable baseline eGFR) and UACR 30, 300, and 1000 mg/g (for continuous variable baseline UACR). ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; and UACR, urine albumin-to-creatinine ratio.

of ASCVD at baseline in the very high KDIGO risk group (50.1%) vs. those in the low (40.6%), moderate (39.8%), or high KDIGO risk groups (41.7%).

The overall incidence rates for all-cause mortality, CV mortality, and non-CV, non-renal mortality in the intention-to-treat population were aligned with KDIGO risk group classification, with the incidence being lower in the low and moderate KDIGO risk groups vs. the high and very high-risk groups (Supplementary material online, *Figure 3*). In general, treatment with finerenone resulted in a numerically lower incidence of all-cause, CV, and non-CV, non-renal mortalities compared with placebo, except for all-cause mortality and CV mortality in patients categorized in the KDIGO very high-risk group and CV mortality in the KDIGO low-risk group. There was no sign of an interaction between the effect of finerenone and KDIGO risk groups for all-cause mortality ($P_{interaction} = 0.1293$) and CV mortality ($P_{interaction} = 0.6361$). A *P* for interaction was not calculated for non-CV, non-renal mortality due to zero cells in the low-risk group causing convergency issues.

Event probability analysis of time to all-cause mortality, CV mortality, or sudden cardiac death at 4 years revealed that the effect of finerenone vs. placebo was largely consistent, irrespective of baseline eGFR in the intention-to-treat population (*Figure 3*). However, the effect of finerenone appeared to be more variable for all three outcomes in patients with higher levels of baseline eGFR (*Figure 3*). Analysis of event probability at 4 years according to baseline UACR revealed that the effect of finerenone vs. placebo was also consistent for time to all-cause mortality, CV mortality, and sudden cardiac death and appeared to be similar across all baseline levels of UACR (*Figure 3*). Analyses of the event probability at 4 years by serum potassium values of patients at month 4 showed that events for all-cause mortality, CV mortality, and sudden cardiac death were lower with finerenone vs. placebo across all levels of serum potassium in the intention-to-treat population. However, the effect of finerenone vs. placebo appeared to be more pronounced at lower levels of serum potassium (*Figure 4*).

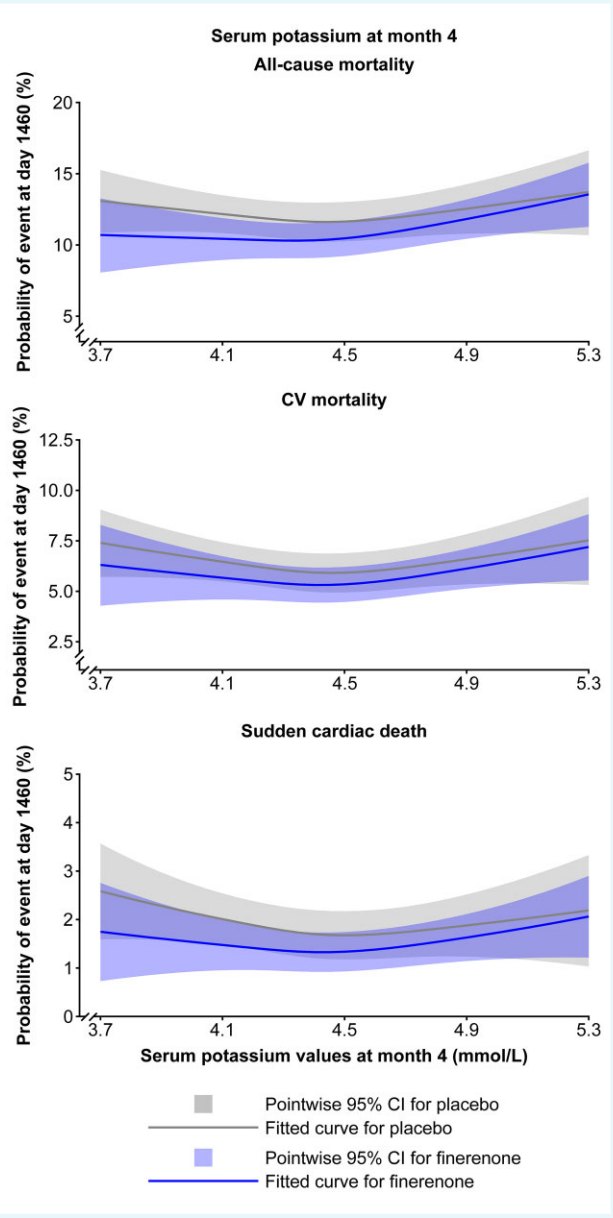


Figure 4 Event probability of time to all-cause mortality, CV mortality, or sudden cardiac death at 4 years according to continuous variable serum potassium at month 4 in the intention-to-treat population. Event probability was analysed after month 4 according to continuous variable serum potassium at month 4. Cox proportional hazards model was fitted with covariates serum potassium values at month 4, treatment, study, ASCVD history, region, sex, race, diuretic use at baseline and continuous covariates age, HbA1c, SBP, baseline UACR (log-transformed), baseline eGFR, and serum potassium at baseline. Splines were used with knots at serum potassium 4.2, 4.4, and 4.8 mmol/L. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; and UACR, urine albumin-to-creatinine ratio.

Discussion

This FIDELITY analysis showed that, although mortality was lower with finerenone vs. placebo, the between-group differences for all-cause mortality and CV mortality were borderline non-significant (i.e. upper bounds of the 95% CI just over unity). When the analysis was restricted to the assessment of mortality in patients while on treatment (including up to 30 days after the last dose of study drug), all-cause mortality and CV mortality were significantly reduced with finerenone vs. placebo. These data show that finerenone may offer protection from mortality in patients with CKD and T2D who continue treatment. Although intention-to-treat analyses remain the mainstay in randomized controlled trials and estimate the effect of drugs in all randomized patients (regardless of treatment adherence),[18] on-treatment analyses estimate the effect of the drugs while being taken by patients and may be a useful metric for patients, prescribers, and other stakeholders.[19]

Around 60% of all deaths observed in the FIDELITY analysis were attributed to CV causes, which is consistent with other studies of patients with CKD and T2D.[2,5] Intention-to-treat analysis of individual causes of CV mortality revealed that a lower risk of sudden cardiac death, the second most frequent cause of CV mortality (following undetermined death), was observed with finerenone vs. placebo. Studies of steroidal MRAs on the incidence of sudden cardiac death are in concordance with these findings. For example, several systematic reviews and meta-analyses have reported a significant reduction in sudden cardiac death in patients with HF, with and without left-ventricular systolic dysfunction or post-myocardial infarction, following treatment with spironolactone, eplerenone, or canrenone.[20–24] Mechanisms

postulated specifically for the protective effect on sudden cardiac death by MRAs in patients with HF include enhancing the effect of ACEis/ARBs on reducing adverse ventricular modelling and suppressing the arrhythmogenic properties of aldosterone.[20] The mechanism by which finerenone reduces the risk of sudden cardiac death in patients with CKD and T2D remains to be elucidated, but the presence of atrial fibrillation and atrial flutter or HF at baseline, among other factors, were identified to have potentially influenced the lower occurrence of sudden cardiac death in the FIDELITY population. Additionally, the low level of hypokalaemia reported with finerenone in FIDELITY may have played a role,[16] given that hypokalaemia was reported to increase the risk of arrhythmias that could lead to sudden cardiac death in patients with HF.[25] Furthermore, the event probability data in this analysis showed that the risk of sudden cardiac death was lower with finerenone in the normal range of serum potassium (4–5 mmol/L) compared with a serum potassium of <4 mmol/L. Therefore, multiple factors were likely to have contributed to the effect of finerenone on sudden cardiac death.

Although there were fewer deaths due to HF with finerenone than with placebo, these events constituted a small proportion of mortality overall. The low proportion of HF deaths observed may be explained by the exclusion of patients with HF with reduced ejection fraction and New York Heart Association Classes II–IV, a population known to have a high mortality risk.[26,27] This is corroborated by the low proportion of patients with a history of HF (7.7%) in the FIDELITY analysis, in whom the incidence rate of mortality among placebo-treated patients was considerably higher (incidence rate per 100 PY, 5.94) than in those without a history of HF (incidence rate per 100 PY, 2.87) and the overall placebo population (incidence rate per 100 PY, 3.10).[16] Interestingly, studies in steroidal MRAs have shown positive effects on mortality in patients with HF with reduced ejection fraction,[28,29] but not in patients with HF and preserved ejection fraction.[30]

Among the remaining non-CV causes of mortality in FIDELITY (around 40%), most were classified as due to infection or malignancy. The incidence of the separate causes of non-CV, non-renal mortality was not significantly different in patients treated with finerenone or placebo. However, a trend towards lower risk of death from malignancy was noted with finerenone. Further investigation on the role of mineralocorticoid receptor signalling in cancer biology would be important to understand this effect. Data on the risk of non-CV, non-renal mortality in patients with CKD and T2D treated with non-steroidal MRAs are scarce. For steroidal MRAs, one population-based study reported that infection-related mortality was higher in patients with stage 5 CKD treated vs. those not treated with spironolactone (incidence rate per 100 PY, 4.4 vs. incidence rate per 100 PY, 1.7, respectively).[31]

Further investigation into the risk of mortality in different patient subpopulations of FIDELITY revealed that there was no indication of an interaction between the effect of finerenone and baseline KDIGO risk group classifications for all-cause mortality and CV mortality. Although analyses of the effect of steroidal MRAs per KDIGO risk groups have not previously been performed, meta-analyses of small studies have provided some insight into the efficacy and safety of steroidal MRAs in patients with early and late CKD.[32] However, the evidence base for MRA use in patients with CKD is more extensive with finerenone compared with steroidal MRAs. Nevertheless, data in our analysis should be interpreted with caution because statistical significance was not reached for the effect of finerenone on all-cause and CV mortality vs. placebo in the intention-to-treat population. In addition, there were a variable number of patients in the KDIGO risk classification categories, with very few patients in the low-risk and moderate-risk groups, thus limiting the interpretation of results in these subgroups.

Time-to-event probability analyses revealed that the effect of finerenone on all-cause mortality, CV mortality, and sudden cardiac death was largely consistent across all levels of baseline UACR. The consistent benefit of finerenone irrespective of baseline UACR levels is an important observation because albuminuria levels are known to correlate with mortality risk in patients with T2D and CKD,[33,34] and this has further been demonstrated by the event probability data in this analysis (*Figure 3*). Similar observations were made for eGFR at baseline and across all levels of potassium at 4 months, although the event probability curves suggested that the treatment effect of finerenone compared with placebo on all three mortality outcomes was most pronounced in patients with a higher baseline eGFR or in patients with lower serum potassium levels at 4 months. A possible explanation for a smaller effect of finerenone on mortality outcomes observed in patients with lower eGFR at baseline could be attributed to the severity of their disease and the associated organ damage, resulting in a patient group that is challenging to treat. This interpretation is supported by meta-analyses conducted in large populations of patients with CKD, where poorer prognosis, a greater risk of end-stage kidney disease (and a lower probability of CKD regression), and a higher incidence of CV outcomes and mortality were reported in patients in high-risk eGFR and UACR categories.[17,35] Nevertheless, the trend towards increased benefits in patients with higher baseline eGFR suggests that early treatment with finerenone may offer a greater likelihood of survival from mortality due to any CV cause.

At baseline, the CKD and T2D population studied here was relatively well controlled with respect to BP, glycaemic control, and the use of CV-protective medications, including optimized renin–angiotensin system inhibitors, as well as frequent use of statins and beta-blockers. The ability to demonstrate a further survival benefit in such a population may therefore have been challenging. It should be noted that the proportion of patients who received an SGLT-2i or a glucagon-like peptide-1 receptor agonist was low at baseline because, at the start of the FIDELIO-DKD and FIGARO-DKD trials, these two therapies were not recommended as standard of care for patients with CKD and/or T2D. Insights into the concomitant treatment of finerenone with an SGLT-2i were recently reported in a subgroup analysis of FIDELITY, and the results indicate that finerenone offers cardiorenal protection in patients with CKD and T2D irrespective of the use of SGLT-2i at baseline.[36]

The main limitation of this analysis is that, while FIDELITY assessed a large number of patients, a median follow-up period of 3 years was relatively short for a robust evaluation of mortality. This may, in part, explain the low overall mortality rate reported in this analysis. Therefore, a clearer outcome will require an extended follow-up period in this patient population. In addition, part of the analysis was performed in the on-treatment patient population, and we remain cautious not to overinterpret these findings. The deaths from undetermined causes also appeared to be frequent. Although the proportion may be marginally above the upper range of other studies,[37] and these were considered as CV mortality using a conservative approach, this is a limitation in the interpretation of causes of mortality in the FIDELITY population. Nevertheless, all deaths in the study were prospectively adjudicated by an independent clinical event committee that would help reduce the chance of bias.

In conclusion, in a prespecified on-treatment analysis, finerenone significantly reduced all-cause mortality and CV mortality compared with placebo in patients with CKD and T2D. The risk of sudden cardiac death was also reduced with finerenone. Finally, the effect of finerenone on all three outcomes was shown to be consistent across all levels of baseline UACR but was most pronounced in patients with a higher baseline eGFR, indicating that earlier initiation of treatment and co-administration of potassium-binding agents, respectively, might be warranted to maximize the protective effects of finerenone in patients with T2D and CKD.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

Data are not currently available.
Will data be available: Yes.
Where: Electronic repository.
When will data availability begin: Date to be confirmed by Bayer.

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