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Analysis

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Finerenone in heart failure and chronic kidney disease with type 2 diabetes: FINE-HEART pooled analysis of cardiovascular, kidney and mortality outcomes

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Cardiovascular-kidney-metabolic syndrome is an emerging entity that connects cardiovascular diseases, chronic kidney disease and diabetes. The non-steroidal mineralocorticoid receptor antagonist finerenone has been studied in three prospective randomized clinical trials of patients with cardiovascular-kidney-metabolic syndrome: FIDELIO-DKD, FIGARO-DKD and FINEARTS-HF. In light of the strong epidemiological overlap and shared mechanistic drivers of clinical outcomes across cardiovascular-kidney-metabolic syndrome, we summarize the efficacy and safety of finerenone on cardiovascular, kidney and mortality outcomes in this pre-specified participant-level pooled analysis. The three trials included 18,991 participants (mean age 67 ± 10 years; 35% women). During 2.9 years of median follow-up, the primary outcome of cardiovascular death occurred in 421 (4.4%) participants assigned to finerenone and 471 (5.0%) participants assigned to placebo (hazard ratio (HR): 0.89; 95% confidence interval (CI): 0.78–1.01; $P = 0.076$). Death from any cause occurred in 1,042 (11.0%) participants in the finerenone arm and in 1,136 (12.0%) participants in the placebo arm (HR: 0.91; 95% CI: 0.84–0.99; $P = 0.027$). Finerenone further reduced the risk of hospitalization from heart failure (HR: 0.83; 95% CI: 0.75–0.92; $P < 0.001$) and the composite kidney outcome (HR: 0.80; 95% CI: 0.72–0.90; $P < 0.001$). While in this pooled analysis the reduction in cardiovascular death was not statistically significant, finerenone reduced the risks for deaths of any cause, cardiovascular events and kidney outcomes. PROSPERO identifier: CRD42024570467.

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Table 1 | Baseline characteristics

	Finerenone	Placebo
	n=9,501	*n*=9,490
Age	67.0±10.0	67.1±10.2
Female	3,390 (35.7%)	3,274 (34.5%)
Race[a]		
Asian	1,910 (20.1%)	1,946 (20.5%)
Black	300 (3.2%)	308 (3.2%)
Other	476 (5.0%)	447 (4.7%)
White	6,815 (71.7%)	6,789 (71.5%)
Region		
Asia	1,808 (19.0%)	1,815 (19.1%)
Eastern Europe	3,001 (31.6%)	2,941 (31.0%)
Latin America	1,041 (11.0%)	1,034 (10.9%)
North America	1,259 (13.3%)	1,261 (13.3%)
Western Europe, Oceania and Others	2,392 (25.2%)	2,439 (25.7%)
Body mass index (kg m^{-2})	30.9±6.1	30.9±6.0
Systolic blood pressure (mmHg)	134.5±14.9	134.4±15.0
Potassium (mmol L^{-1})	4.4±0.5	4.4±0.5
eGFR (mL min^{-1} 1.73 m^{-2})	58.9±21.0	59.1±21.3
eGFR category		
<25 mL min^{-1} 1.73 m^{-2}	100 (1.1%)	94 (1.0%)
25 to <45 mL min^{-1} 1.73 m^{-2}	2,742 (28.9%)	2,782 (29.3%)
45 to <60 mL min^{-1} 1.73 m^{-2}	2,513 (26.5%)	2,469 (26.0%)
≥60 mL min^{-1} 1.73 m^{-2}	4,145 (43.6%)	4,143 (43.7%)
UACR (mg g^{-1})	283 (46–836)	293 (47–855)
Albuminuria category		
A1 (<30 mg g^{-1})	1,885 (20.1%)	1,856 (19.8%)
A2 (30 to <300 mg g^{-1})	2,910 (31.0%)	2,883 (30.7%)
A3 (≥300 mg g^{-1})	4,602 (49.0%)	4,646 (49.5%)
Hemoglobin A1c (%)	7.3±1.4	7.3±1.4
AF on electrocardiogram	1,449 (15.3%)	1,379 (14.5%)
History of HF[b]	3,488 (36.7%)	3,520 (37.1%)
Baseline CKD[c]	7,949 (83.7%)	7,929 (83.6%)
History of DM[d]	7,715 (81.2%)	7,714 (81.3%)
Background medication use		
Diuretics	6,291 (66.2%)	6,340 (66.8%)
ACEi/ARB/ARNI	8,866 (93.3%)	8,860 (93.4%)
Aspirin	4,145 (43.6%)	4,171 (44.0%)
Statins	6,687 (70.4%)	6,750 (71.1%)
SGLT-2 inhibitors	829 (8.7%)	861 (9.1%)
GLP-1 receptor agonists	576 (6.1%)	534 (5.6%)
Potassium-lowering therapies[e]	99 (1.0%)	96 (1.0%)

A1, A2 and A3, albuminuria categories; ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; DM, diabetes mellitus. [a]Represents self-reported race. Participants choosing not to disclose race or who self-identified as multiple races are included in the 'Other' category for descriptive purposes. [b]HF includes all participants in FINEARTS-HF and those with investigator-reported history of HF in the primary CKD outcomes trials (FIDELIO-DKD and FIGARO-DKD). [c]CKD includes all participants in the primary CKD outcomes trials (FIDELIO-DKD and FIGARO-DKD) and participants in FINEARTS-HF with baseline eGFR of <60 mL min^{-1} 1.73 m^{-2}. [d]Diabetes includes all participants in the primary CKD outcomes trials (FIDELIO-DKD and FIGARO-DKD) and those with a history of diabetes in FINEARTS-HF. [e]Includes patiromer, sodium polystyrene sulfonate and calcium polystyrene sulfonate.

Cardiovascular diseases, chronic kidney disease (CKD) and metabolic conditions frequently occur in the same individual and may share common pathophysiological pathways of disease onset and progression[1–3]. This cardiovascular-kidney-metabolic (CKM) overlap is increasingly recognized, and there is potential for individual therapies to simultaneously improve multiple adjacent disease states[4]. Activation of the mineralocorticoid receptor is a well-recognized driver of systemic and target organ inflammation and fibrosis in these disease states[5–7]. Steroidal mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, target these shared pathways, but their widespread use has been limited, especially in patients with CKM multimorbidity[8]. Gaps in implementation of steroidal mineralocorticoid receptor antagonists in heart failure (HF) are, in part, related to safety concerns due to hyperkalemia and worsening kidney function[9].

Finerenone is a selective and potent non-steroidal mineralocorticoid receptor antagonist[5,10–13] that may have lower risks of hyperkalemia and worsening kidney function compared to spironolactone[14]. Finerenone has been shown to reduce the risk of cardiovascular events and kidney failure in patients with CKD with type 2 diabetes (T2D)[15,16] and has recently been shown to reduce worsening HF events in patients with HF with mildly reduced or preserved ejection fraction[17]. However, none of these trials was individually powered to evaluate treatment effects on less frequent cardiovascular-kidney outcomes, such as cardiovascular death or efficacy in key subgroups, including those with overlapping CKM conditions. A previous pooled analysis of the CKD with T2D trials showed that finerenone reduced major adverse cardiovascular events by 14% and a kidney composite outcome by 22% but remained underpowered in the evaluation of mortality outcomes[18]. Broadening this pooled population to encompass participants from the recently completed FINEARTS-HF trial will enhance precision on a range of safety and efficacy outcomes and allow evaluation of previously understudied subpopulations.

In light of the strong epidemiological overlap and shared mechanistic drivers, pooled integrated assessment of these CKM trials was pre-specified in a participant-level analysis of three phase 3 global, multicenter, double-blind, placebo-controlled randomized clinical trials of finerenone (FINE-HEART).

Results

Overall, FINE-HEART comprised 18,991 participants from these three trials. Baseline clinical profiles and treatment patterns are summarized for the overall pooled population (Table 1) and by individual trial (Extended Data Table 4). Mean age was 67 ± 10 years; 35.1% were women; and participants were enrolled across all major geographic regions. Participants were at high risk for CKD progression (Extended Data Fig. 2) with either reduced estimated glomerular filtration rate (eGFR) (30.1% with eGFR < 45 and 26% with eGFR 45–60 ml min^{-1} 1.73 m^{-2}) and/or albuminuria (30.8% with 'A2' urine albumin creatinine ratio (UACR) 30–299 mg g^{-1} and 49.2% with 'A3' UACR ≥ 300 mg g^{-1}). In total, 2,307 (12.1%) participants had all CKM conditions (HF, CKD and diabetes) (Extended Data Fig. 3). At baseline, 1,690 (8.9%) participants were co-treated with a sodium–glucose co-transporter-2 (SGLT2) inhibitor, and 1,110 (5.8%) participants were co-treated with a glucagon-like peptide-1 receptor agonist (GLP-1RA). Baseline characteristics and concurrent medical management were well balanced between treatment arms (Table 1). Most participants were titrated to a final dose of 20 mg (4,645 (69.8%) in the placebo arm and 4,248 (63.6%) in the finerenone arm), and some (exclusively in FINEARTS-HF) were titrated to 40 mg (920 (13.8%) in the placebo arm and 832 (12.5%) in the finerenone arm).

Median duration of follow-up was 2.6 years (FIDELIO-DKD), 3.4 years (FIGARO-DKD) and 2.6 years (FINEARTS-HF). Median follow-up of the pooled patient population was 2.9 years. The primary endpoint of cardiovascular death occurred in 421 (4.4%) participants in the finerenone arm and in 471 (5.0%) participants in the placebo arm (hazard ratio (HR): 0.89; 95% confidence interval (CI): 0.78–1.01; $P = 0.076$)

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Outcomes	Finerenone (*n* = 9,501) No. of patients with event (%)	IR per 100 py	Placebo (*n* = 9,490) No. of patients with event (%)	IR per 100 py	HR (95% CI)	*P* value
Primary endpoint						
CV death (excluding undetermined death)	421 (4.4)	1.5	471 (5.0)	1.7	0.89 (0.78–1.01)	0.076
Pre-specified sensitivity analysis: CV death (including undetermined death)	627 (6.6)	2.3	703 (7.4)	2.6	0.88 (0.79–0.98)	0.025
Secondary endpoints						
Kidney composite endpoint	557 (5.9)	2.3	685 (7.2)	2.8	0.80 (0.72–0.90)	<0.001
HF hospitalization	705 (7.4)	2.7	839 (8.8)	3.2	0.83 (0.75–0.92)	<0.001
CV death or HF hospitalization	1,009 (10.6)	3.9	1,168 (12.3)	4.5	0.85 (0.78–0.93)	<0.001
New-onset atrial fibrillation	286 (3.9)	1.4	345 (4.7)	1.6	0.83 (0.71–0.97)	0.019
Major adverse cardiovascular events	1,428 (15.0)	5.6	1,554 (16.4)	6.2	0.91 (0.85–0.98)	0.010
All-cause death	1,042 (11.0)	3.8	1,136 (12.0)	4.2	0.91 (0.84–0.99)	0.027
All-cause hospitalization	4,261 (44.8)	21.1	4,401 (46.4)	22.2	0.95 (0.91–0.99)	0.025
All-cause death or all-cause hospitalization	4,467 (47.0)	22.2	4,653 (49.0)	23.5	0.94 (0.91–0.98)	0.007

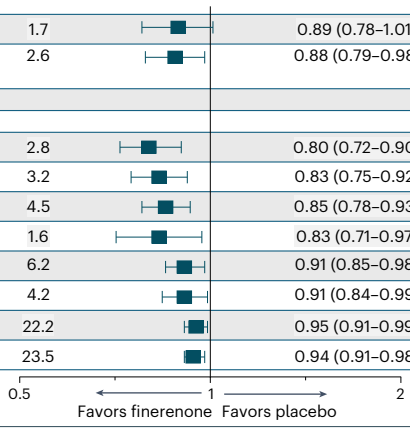

Fig. 1 | Efficacy outcomes. The primary efficacy outcome was cardiovascular death (deaths of undetermined causes were excluded). Pre-specified sensitivity analysis of the primary efficacy outcome considered deaths of undetermined causes as having a cardiovascular cause. The kidney composite outcome was defined as a sustained decrease in eGFR to ≥50% from baseline, sustained decline in eGFR to <15 ml min^{-1} 1.73 m^{-2}, kidney failure and death due to kidney failure. Major adverse cardiovascular events included cardiovascular death or a non-fatal cardiovascular event (HF hospitalization, myocardial infarction or stroke). The composite of all-cause death or all-cause hospitalization was defined post hoc. All primary and secondary outcomes were analyzed as time to first outcomes using a stratified Cox proportional hazards model including the study intervention group as a fixed effect and stratified by geographic region and individual trial. All two-sided *P* values are reported without adjustment for multiple comparisons. The bars represent 95% CIs around each treatment effect point estimate. CV, cardiovascular; IR, incidence rate.

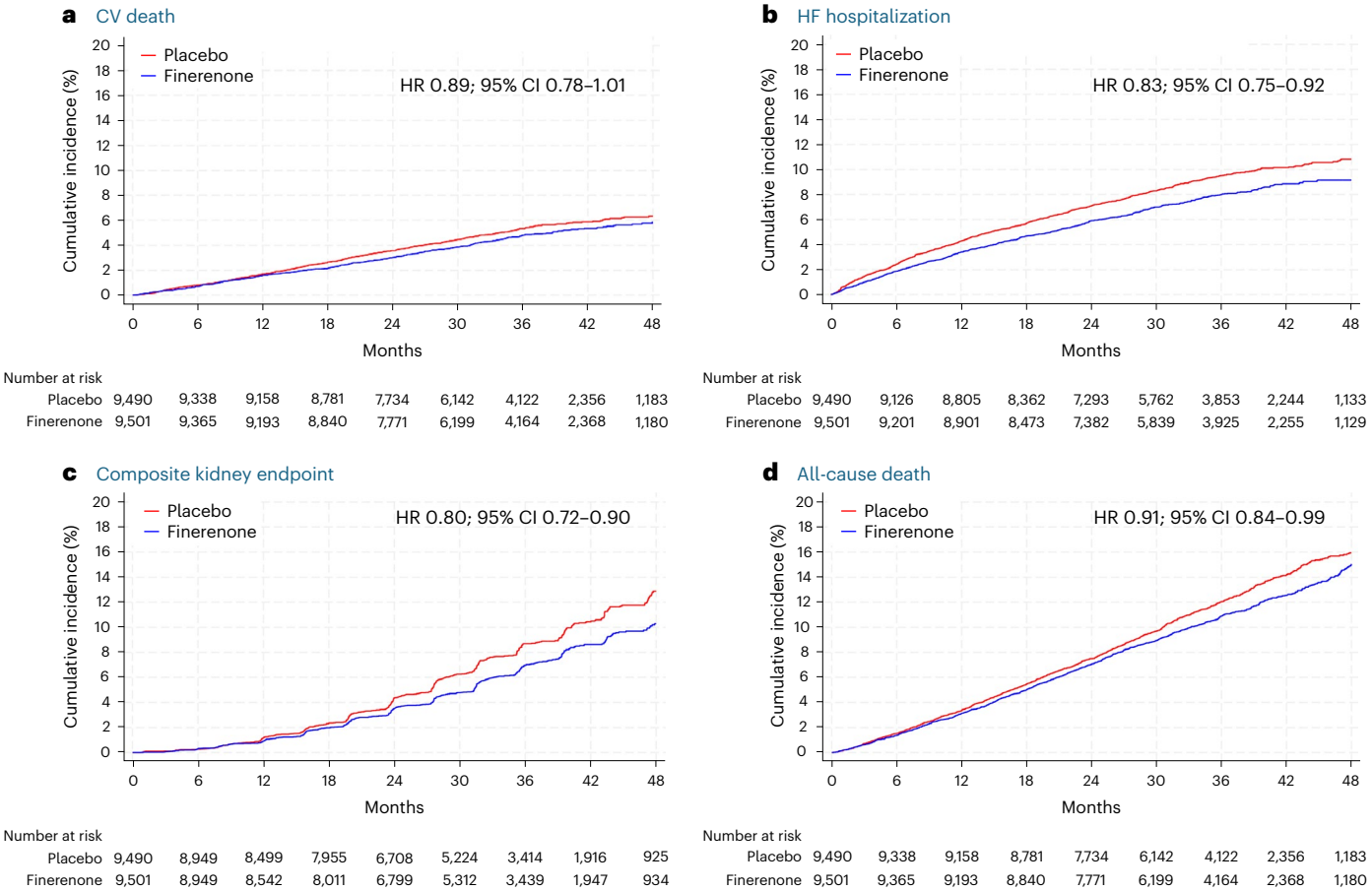

Fig. 2 | Cumulative incidence of key efficacy outcomes. Incidence of cardiovascular (CV) death (primary outcome) (**a**); HF hospitalization (**b**); kidney composite outcome (sustained decrease in eGFR to ≥50% from baseline, sustained decline in eGFR to <15 ml min^{-1} 1.73 m^{-2}, kidney failure and death due to kidney failure) (**c**); and all-cause death (**d**).

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Table 2 | Cause-specific death

Cause of death	Finerenone		Placebo		Total	
	n	Rate per 100 py	*n*	Rate per 100 py	*n*	Rate per 100 py
All-cause death	1,042	3.8	1,136	4.2	2,178	4.0
Cardiovascular causes						
Sudden	188	0.7	230	0.9	418	0.8
Heart failure	92	0.3	113	0.4	205	0.4
Stroke	47	0.2	59	0.2	106	0.2
Myocardial infarction	35	0.1	37	0.1	72	0.1
Cardiovascular procedural	12	0.0	7	0.0	19	0.0
Other cardiovascular related	47	0.2	25	0.1	72	0.1
Non-CV causes						
Infection	194	0.7	188	0.7	382	0.7
Malignancy	121	0.4	149	0.6	270	0.5
Renal	4	0.0	6	0.0	10	0.0
Other non-cardiovascular related	96	0.3	90	0.3	186	0.3
Undetermined	206	0.8	232	0.9	438	0.8

py, patient years.

with consistent findings in pre-specified sensitivity analysis including both cardiovascular deaths and undetermined deaths (6.6% versus 7.4%; HR: 0.88; 95% CI: 0.79–0.98; $P = 0.025$) (Fig. 1). Effects on cardiovascular death were consistent across individual trials: FIDELIO-DKD (HR: 0.90; 95% CI: 0.65–1.23); FIGARO-DKD (HR: 0.81; 95% CI: 0.62–1.04); and FINEARTS-HF (HR: 0.93; 95% CI: 0.78–1.11); $P_{interaction} = 0.68$ (Extended Data Fig. 4). Deaths from any cause occurred in 1,042 (11.0%) participants in the finerenone arm and in 1,136 (12.0%) participants in the placebo arm (HR: 0.91; 95% CI: 0.84–0.99; $P = 0.027$) (Fig. 2). A complete accounting of cause-specific death by treatment arm is shown in Table 2.

Finerenone reduced the risk of the composite kidney outcome whether defined inclusive of a sustained decrease in eGFR to ≥50% from baseline (HR: 0.80; 95% CI: 0.72–0.90; $P < 0.001$) or a sustained decrease in eGFR to ≥57% from baseline (HR: 0.79; 95% CI: 0.70–0.91; $P < 0.001$). These kidney effects appeared to be driven by FIDELIO-DKD and FIGARO-DKD (Extended Data Fig. 4). The incidences of the individual components of the kidney composite endpoint are displayed in Extended Data Table 5. Finerenone reduced the risk of hospitalizations due to HF alone (HR: 0.83; 95% CI: 0.75–0.92; $P < 0.001$) and the composite of cardiovascular death or HF hospitalization (HR: 0.85; 95% CI: 0.78–0.93; $P < 0.001$). Hospitalizations of any cause were also lower with finerenone compared to placebo (HR: 0.95; 95% CI: 0.91–0.99; $P = 0.025$). Finerenone further reduced the risk of the composite of all-cause death or all-cause hospitalization (HR: 0.94; 95% CI: 0.91–0.98; $P = 0.007$). Additional risk reductions were observed for the prevention of new-onset atrial fibrillation and major adverse cardiovascular events (Fig. 1).

Treatment effects on cardiovascular death were generally consistent across the 16 subgroups examined (Fig. 3). The efficacy of finerenone on cardiovascular death was consistent across the range of eGFR ($P_{interaction} = 0.32$) and UACR ($P_{interaction} = 0.55$) (Extended Data Fig. 5). Treatment effects on cardiovascular death were also consistent across a range of CKM disease burden: one condition (HR: 0.93; 95% CI: 0.65–0.1.33); two conditions (HR: 0.87; 95% CI: 0.74–1.03); and three conditions (HR: 0.91; 95% CI: 0.71–1.18); $P_{interaction} = 0.94$.

Incidences of any serious adverse event were lower with finerenone than placebo (34.6% versus 36.6%), although incidences of serious adverse events leading to drug discontinuation were slightly higher with finerenone (5.4% versus 4.6%). Laboratory-defined hyperkalemia was increased, whereas laboratory-defined hypokalemia was decreased, with finerenone. Incidences of investigator-reported hyperkalemia leading to permanent treatment discontinuation (1.3% versus 0.5%) and hyperkalemia-related hospitalization (0.8% versus 0.2%) were higher with finerenone. There were no deaths related to hyperkalemia and no between-group differences in incidences of acute kidney injury (Table 3).

Discussion

This participant-level pooled analysis, FINE-HEART, represents, to our knowledge, the largest analysis of the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist finerenone across the CKM spectrum. Although this pooled analysis did not demonstrate a significant reduction in the primary outcome of cardiovascular death, this result was sensitive to the definition of cardiovascular death based on the classification of deaths of undetermined causes. As such, we placed greater confidence in the outcome of all-cause death, which was reduced with finerenone with nominal significance. This mortality signal with finerenone was further substantiated by clinically relevant benefits observed across a broad range of other cardiovascular-kidney outcomes, including kidney disease progression, HF hospitalizations, all-cause hospitalizations, new-onset atrial fibrillation and major adverse cardiovascular events. Treatment effects were consistent across all tested clinical subgroups, including those with multiple, intersecting CKM conditions. No new or unexpected safety signals were uncovered in this pooled analysis with a well-characterized modestly higher risk of hyperkalemia but overall lower incidences of serious adverse events and no excess risk of acute kidney injury with finerenone. Taken together, these data suggest the potential of finerenone to prevent or delay morbidity and mortality across a wide range of CKM conditions while being safe and well tolerated.

Finerenone is approved for use in patients with CKD and T2D. Although several major multi-specialty guidelines strongly recommend finerenone to delay CKD progression and prevent HF events in people with CKD with T2D[19–21], the latest Kidney Disease: Improving Global Outcomes (KDIGO) guideline[22] has offered a class 2A recommendation potentially related to residual uncertainties regarding the mortality effects of finerenone in the FIDELIO-DKD and FIGARO-DKD trials. Furthermore, according to the guideline, its use is to be considered in patients already on standard-of-care therapies, such as maximally tolerated renin–angiotensin system inhibitors and/or SGLT2 inhibitors. These pooled data did not identify heterogeneity

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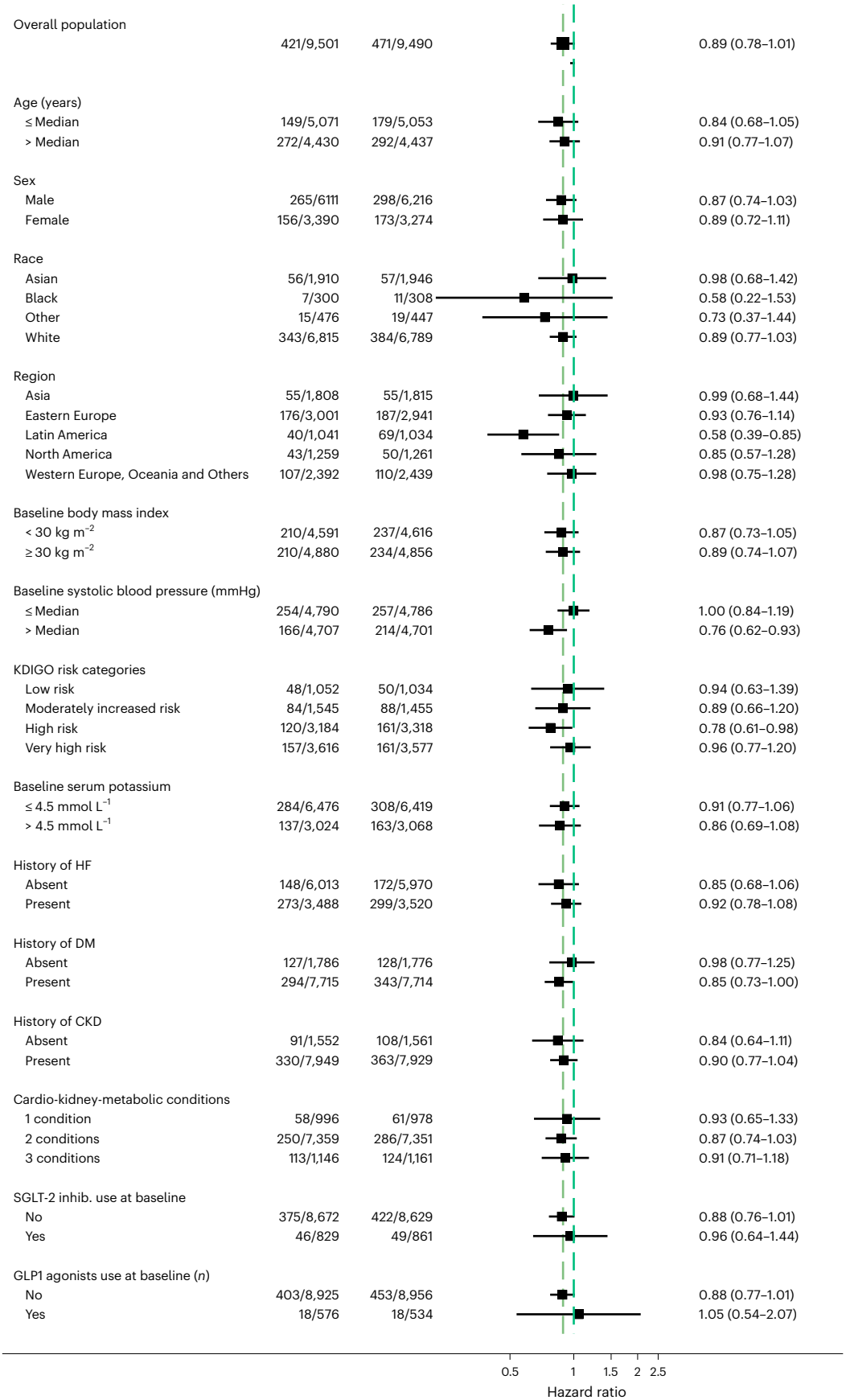

Fig. 3 | Subgroup forest plot for primary outcome (CV death). The median age was 68 years, and the median systolic blood pressure was 135 mmHg. For each patient, the presence of CKM conditions was summed for the following comorbidities: CKD, HF and/or DM. The bars represent 95% CIs around each treatment effect point estimate. CV, cardiovascular; DM, diabetes mellitus.

Table 3 | Safety outcomes

	Finerenone	Placebo
	n=9,482	*n*=9,467
Any serious adverse event	3,283 (34.6%)	3,463 (36.6%)
Any adverse event leading to treatment discontinuation	515 (5.4%)	434 (4.6%)
Any potassium >5.5 mmol L^{-1} [a]	1,535 (16.5%)	714 (7.7%)
Any potassium >6.0 mmol L^{-1} [a]	311 (3.3%)	133 (1.4%)
Any potassium <3.5 mmol L^{-1} [a]	448 (4.8%)	938 (10.1%)
Hyperkalemia[b]	1,216 (12.8%)	586 (6.2%)
Hyperkalemia leading to treatment discontinuation[b]	123 (1.3%)	43 (0.5%)
Hyperkalemia leading to hospitalization[b]	80 (0.8%)	17 (0.2%)
Hyperkalemia leading to death[b]	0 (0.0%)	0 (0.0%)
Acute kidney injury	345 (3.6%)	316 (3.3%)
Acute kidney injury leading to treatment discontinuation	15 (0.2%)	12 (0.1%)
Acute kidney injury leading to hospitalization	143 (1.5%)	116 (1.2%)
Systolic blood pressure <100 mmHg	1,040 (11.1%)	651 (7.0%)
Gynecomastia or breast hyperplasia	16 (0.2%)	19 (0.2%)

Treatment-emergent adverse events are defined as any adverse event occurring in any patient who has received at least one dose of study drug and within 3 d of permanent discontinuation. This safety table includes one patient who was randomized to placebo but who actually received finerenone. [a]Based on central laboratory measurements of potassium levels. [b]Based on investigator-reported adverse events.

with finerenone's effects on cardiovascular death by background use of SGLT2 inhibitors or GLP-1RA, although the statistical power of these subgroup findings was limited. This pooled analysis bolsters recent calls for the combination use of finerenone alongside these therapies as foundational 'pillars' of care to maximize improvements in cardiovascular-kidney outcomes[23,24]; additional evidence will be needed to inform the expected efficacy and safety of various combinations of risk-lowering therapies.

Finerenone was shown to robustly reduce the kidney composite outcome by 20% in this pooled analysis, driven by benefits observed in FIDELIO-DKD and FIGARO-DKD. FINEARTS-HF enrolled a primary HF population with some co-existing kidney disease but with relatively low levels of albuminuria; therefore, CKD progression over a relatively short period of follow-up was difficult to evaluate. It is reassuring that finerenone did not show an increase in reports of acute kidney injury, despite the high baseline kidney risk profile of the patient population and the varied clinical care settings of therapeutic initiation.

Although each trial had broad eligibility criteria, some groups were understudied in individual trials. For instance, both FIGARO-DKD and FIDELIO-DKD exclusively enrolled participants with CKD and T2D with albuminuria. FINEARTS-HF provides complementary evidence related to finerenone's therapeutic effects in previously understudied populations, including those without diabetes (~60% of trial enrollment), those without CKD and those without significant urinary albumin excretion (>60% of the trial with UACR <30 mg g^{-1}). FINEARTS-HF exclusively enrolled patients with symptomatic HF across clinical care settings, whereas FIDELIO-DKD and FIGARO-DKD specifically excluded patients with symptomatic HF with reduced ejection fraction. It is noteworthy that FIDELIO-DKD and FIGARO-DKD did enroll 5–10% of patients with HF with mildly reduced or preserved ejection fraction, emphasizing the overlap across these trials. These pooled data demonstrate that finerenone's benefits extend to patients with different degrees of CKM multimorbidity and across broad patient profiles and enhance precision of estimates of risk reductions beyond previous analyses[18]. The diverse spectrum of benefits on HF, arrhythmia, atherosclerotic risk and kidney disease progression also underscores the systemic actions of finerenone in attenuating the adverse multi-organ effects of mineralocorticoid receptor overactivation[5].

A key strength of this pooled analysis was access to individual participant-level data from all phase 3 trials conducted to date with finerenone, which allowed harmonization of data elements related to baseline clinical characteristics, outcomes and subgroups. Major efficacy outcomes were independently adjudicated, and safety assessments were conducted with aligned definitions in a standardized fashion. As undetermined deaths are variably handled across trials of CKM conditions, including in the three trials examined in this pooled study, separate analyses were carried out for cardiovascular death excluding and including these deaths.

This pooled analysis is subject to several limitations. The findings were derived from randomized clinical trials with specific inclusion and exclusion criteria and, thus, may not be generalizable to all populations treated in clinical practice. Despite the large global population studied, enrollment of select groups, such as Black patients, remained limited. Certain data elements were not consistently available across trials to allow for pooling. For instance, urgent HF visits, which were included as a part of the FINEARTS-HF primary outcome, were not collected in FIDELIO-DKD and FIGARO-DKD. Background use of SGLT2 inhibitors and GLP-1RA was only modest, limiting firm conclusions of the additive effects of finerenone. No adjustment was made for testing of multiple comparisons. Finally, not all trials contributed equally to each of the subgroups examined; for instance, only FINEARTS-HF included patients who did not have diabetes.

While in this pooled analysis the reduction in cardiovascular death was not statistically significant, finerenone reduced the risks for deaths of any cause, cardiovascular events and kidney outcomes while being safe and well tolerated. The totality of the evidence thus supports the disease-modifying potential of finerenone in broad, high-risk patient populations encompassing cardiovascular, kidney and metabolic diseases.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03264-4.

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Methods

Search strategy and trial selection

We conducted a participant-level pooled analysis of two trials of CKD and T2D (FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; NCT02540993) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; NCT02545049)) and a trial of patients with HF (FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; NCT04435626)) that included patients with and without diabetes. The designs[25–27] and primary results[15–17] of each of the three trials have been published. Key design elements of each of the trials are summarized in Extended Data Table 1. We further conducted a systematic review of the literature using PubMed and MEDLINE to ensure that other relevant trials were not missed. We searched for randomized clinical trials of finerenone published from database inception to 24 July 2024. The following string was used in the PubMed/MEDLINE pre-specified search query to identify potential studies to be included in the meta-analysis:

('finerenone'[Extended Data Concept] OR 'finerenone'[All Fields]) AND (randomizedcontrolledtrial[Filter]). The pre-specified search query, which was run on 24 July 2024, did not identify any additional phase 3 trials that met criteria for inclusion (Extended Data Fig. 1). Data from the FINEARTS-HF trial were unpublished at the time of analysis and were included with permission from the steering committee and trial sponsor.

Design of FIDELIO-DKD and FIGARO-DKD

In brief, both FIDELIO-DKD and FIGARO-DKD trials enrolled adults (≥18 years) with T2D and CKD across 48 countries. FIDELIO-DKD required a UACR of 30 to <300 mg g^{-1}, an eGFR of 25 to <60 ml min^{-1} 1.73 m^{-2} and a history of diabetic retinopathy or a UACR of 300–5,000 mg g^{-1} and an eGFR of 25 to <75 ml min^{-1} 1.73 m^{-2}. FIGARO-DKD required a UACR of 30 to <300 mg g^{-1} and an eGFR of 25–90 ml min^{-1} 1.73 m^{-2} or a UACR of 300–5,000 mg g^{-1} and an eGFR of ≥60 ml min^{-1} 1.73 m^{-2}. Both trials required a serum potassium level of ≤4.8 mmol L^{-1} for enrollment. Renin–angiotensin system inhibitor use and dosing were optimized before screening during run-in phases (lasting 4–16 weeks) in both trials. Patients with symptomatic HF with reduced ejection fraction were excluded, but those with HF and higher ejection fraction were eligible.

Design of FINEARTS-HF

FINEARTS-HF enrolled adults (≥40 years) with symptomatic HF with mildly reduced or preserved ejection fraction across 37 countries. Key inclusion criteria included left ventricular ejection fraction ≥40%, elevated natriuretic peptides (adjusted based on atrial fibrillation status and clinical setting of screening), evidence of structural heart disease and recent diuretic use for at least 30 d. Patients were required to have an eGFR of ≥25 ml min^{-1} 1.73 m^{-2} and a serum potassium level of ≤5.0 mmol L^{-1} for enrollment. Participants could be enrolled regardless of clinical care setting (whether hospitalized, recently hospitalized or ambulatory).

All participants were randomly allocated to finerenone or placebo with initial dosing determined based on kidney function. The initial dose was 10 mg for patients with an eGFR of <60 ml min^{-1} 1.73 m^{-2}, titrated up to a target dose of 20 mg once daily as tolerated. Participants with an eGFR of ≥60 ml min^{-1} 1.73 m^{-2} were started at the target dose of 20 mg once daily. In FINEARTS-HF, participants with an eGFR of >60 ml min^{-1} 1.73 m^{-2} were started on 20 mg and could be titrated up to 40 mg once daily as tolerated, whereas 20 mg was the target dose for patients with an eGFR of ≤60 ml min^{-1} 1.73 m^{-2}. As dose-dependent effects of finerenone have been observed on natriuretic peptide levels in the preceding phase 2 program of patients with worsening HF[28], FINEARTS-HF examined a higher target maintenance dose of 40 mg (in those with an eGFR of >60 ml min^{-1} 1.73 m^{-2}) than in FIDELIO-DKD and FIGARO-DKD. The trial protocols were approved by ethics committees or institutional review boards at all participating sites, and all patients provided explicit written informed consent.

FINE-HEART pooling strategy

Individual participant-level data were accessed and pooled with harmonized data elements for baseline characteristics and clinical outcomes (Extended Data Table 2). All participants randomized in each of the three trials were considered for this pooled analysis with only patients with critical Good Clinical Practice violations excluded. A total of 160 randomized patients (60 patients in FIDELIO-DKD, 85 patients in FIGARO-DKD and 15 patients in FINEARTS-HF) were prospectively excluded before database lock from all analyses because of critical Good Clinical Practice violations or due to re-randomization of the same subject. In addition, 36 participants in FIDELIO-DKD and FIGARO-DKD were confirmed to have critical Good Clinical Practice violations after database lock. These 196 participants were excluded from all efficacy and safety analysis in FINE-HEART. The final sample size was 18,991 participants.

FINE-HEART pooled analysis outcomes

All efficacy outcomes were analyzed in randomized patients under intention-to-treat principles, and all safety outcomes were analyzed in randomized patients who had taken at least one dose of the study drug. All deaths were adjudicated by independent clinical endpoint committees in each of the respective trials included in this pooled analysis (specific adjudication criteria included in the Supplementary Methods).

The pre-specified primary outcome for FINE-HEART was time to cardiovascular death. The definition of cardiovascular death differed slightly among the three trials and was harmonized for FINE-HEART as time to cardiovascular death (excluding undetermined deaths) (Extended Data Table 2). Other pre-specified outcomes included a kidney composite outcome (defined as a sustained decrease in eGFR to ≥50% from baseline, sustained decline in eGFR to <15 ml min^{-1} 1.73 m^{-2}, kidney failure and death due to kidney failure), HF hospitalization, composite of cardiovascular death or HF hospitalization, new-onset atrial fibrillation, major adverse cardiovascular events (a composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization or cardiovascular death), all-cause death and hospitalization for any reason. The kidney composite endpoint inclusive of a sustained decrease in eGFR to ≥57% from baseline (corresponding to a doubling of serum creatinine) was additionally reported. The composite of all-cause death or all-cause hospitalization was defined post hoc to describe the total burden or morbidity and mortality. Select treatment-emergent adverse events related to hyperkalemia, acute kidney injury, hypotension and gynecomastia were additionally reported. The primary outcome (cardiovascular death) was assessed across key subgroups, including age, sex, race, region, baseline body mass index, baseline systolic blood pressure, KDIGO risk, baseline serum potassium levels, baseline eGFR, baseline UACR, history of HF, history of diabetes, presence of CKD, number of CKM conditions (CKD, HF and/or diabetes) and baseline use of SGLT2 inhibitors or GLP-1RA.

Statistical analysis

All primary and secondary outcomes were analyzed as time to first outcomes using a stratified Cox proportional hazards model including the study intervention group as a fixed effect and stratified by geographic region and individual trial (Extended Data Table 2). All treatment effect estimates are presented as HRs with associated 95% CIs. Select primary and secondary outcomes were additionally graphically displayed using Kaplan–Meier methods. There was no multiple testing strategy; namely, testing for secondary outcomes continued even if results for the primary outcome were neutral or negative. A pre-specified sensitivity analysis was conducted for the primary outcome that considered deaths of undetermined causes to be cardiovascular deaths in all three

trials. Treatment effects on cardiovascular death were assessed across all pre-specified subgroups. Incidence rates of cardiovascular death as a function of baseline eGFR and log-transformed UACR were estimated separately for each treatment arm using Poisson regression models, allowing for potentially nonlinear relationships using restricted cubic splines with three knots. The treatment effect of finerenone was then estimated as the ratio of these two group-specific estimates.

The statistical analysis plan for this pooled analysis was pre-specified, and the protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42024570467) before unblinding the FINEARTS-HF trial. All three trials were assessed as high quality with a low risk of bias before pooling (Extended Data Table 3). The trials included in this pooled analysis were funded by Bayer AG. Trial steering committees designed and oversaw their conduct in collaboration with the sponsor. However, the primary analyses, interpretation of the data and initial manuscript drafting were conducted independently by the academic teams. Statistical analyses were conducted using STATA version 18 software.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

For each of the three clinical trials (FIDELIO-DKD, FIGARO-DKD and FINEARTS-HF), Bayer (the sponsor) commits to sharing, upon reasonable request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data and protocols. Interested researchers can use https://vivli.org/ to request access to anonymized patient-level data and supporting documents from clinical studies. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel, with scope and conditions laid out as on https://vivli.org/ourmember/bayer/.

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Author contributions

All authors made substantial contributions to the conceptualization and design of the study. B.L.C. and P.S.J. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. P.S. and J.L.-F. cross-verified all analytic output. M.V. wrote the first draft of the manuscript. All authors contributed to data interpretation and writing of the final version of the manuscript, and all authors were responsible for the decision to submit the manuscript for publication.

Competing interests

M.V. has received research grant support, served on advisory boards or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Bristol Myers Squibb, 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. G.F. has received lecture fees from Bayer, Boehringer Ingelheim, Servier and Novartis; trial committee membership fees from Bayer, Boehringer Ingelheim, Servier, Impulse Dynamics, Vifor and Medtronic; consulting fees from Cardior and Novo Nordisk; and research grants from the European Union. B.L.C. has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia and Rocket and has served on a data and safety monitoring board (DSMB) for Novo Nordisk. A.S.S. 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 and Zydus. P.S.J. reports speaker fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications and Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim and Novartis; and research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices and Roche Diagnostics. P.S.J.'s employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis and Novo Nordisk. Director of the Global Clinical Trial Partners Ltd. A.D. has no financial conflicts to report. M.B. is a full-time employee of Bayer AG. P.K. is a full-time employee of Bayer AG. He is also a co-inventor of finerenone and holds US and European patents relating to finerenone (US8436180B2 and EP2132206B1). P.S. is an employee of Bayer AG. J.L.-F. is a full-time employee of Bayer plc, Research & Development, Pharmaceuticals. P.V. is an employee of Bayer AG. C.S.P.L. 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, Medscape/WebMD Global, Merck, Novartis, Novo Nordisk, Prosciento, Quidel Corporation, Radcliffe Group, Recardio ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and is a co-founder and non-executive director of Us2.ai. M.S. has served on advisory boards for and has received consultancy fees and honoraria from Novartis, Abbott, Merck, Merck Sharp & Dohme, Vifor, AstraZeneca, Cardurion, Novonordisk, Bayer and Boehringer Ingelheim. S.J.S. has received research grants from the National Institutes of Health (NIH) (U54 HL160273, X01 HL169712, R01 HL140731 and R01 HL149423), the American Heart Association (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, Eli Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor,

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Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-024-03264-4.

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Correspondence and requests for materials should be addressed to Scott D. Solomon.

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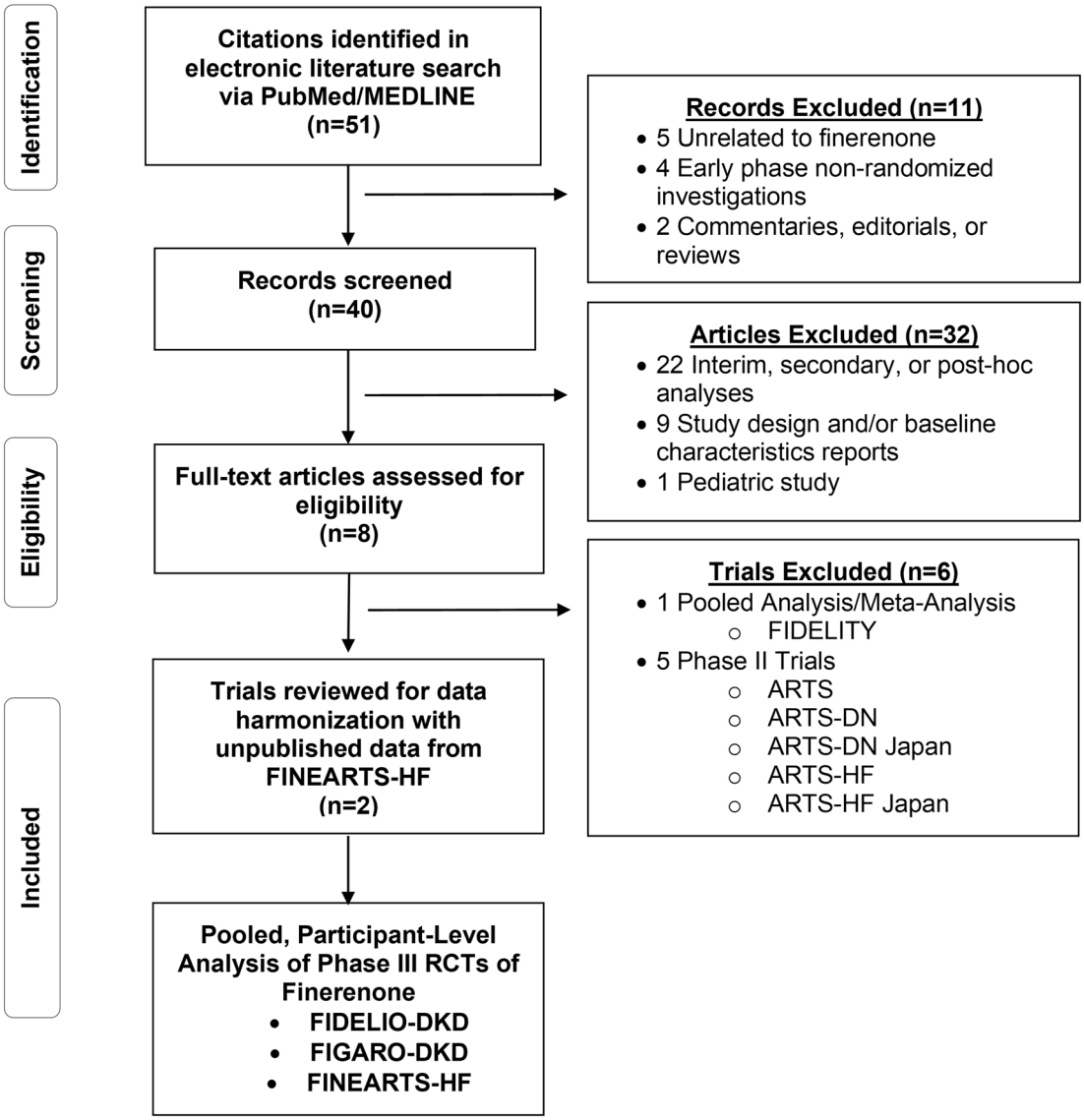


Extended Data Fig. 1 | Systematic Search of the Literature to Identify Eligible Trials for Inclusion in FINE-HEART. We conducted a systematic review of the literature using PubMed and MEDLINE to ensure that relevant trials were not missed to be included in this pooled analysis.

https://doi.org/10.1038/s41591-024-03264-4

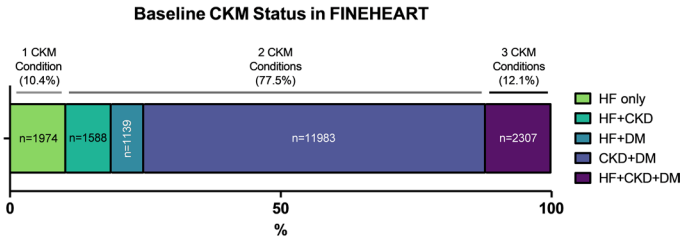
FINE-HEART (n=18,781 with Available Data)

Estimated GFR (mL/min/1.73m²)				UACR (mg/g) A1 Normal to Mildly Increased <30	UACR (mg/g) A2 Moderately Increased 30 to <300	UACR (mg/g) A3 Severely Increased ≥300
	G1	Normal or High	≥90	2.0%	1.8%	6.1%
	G2	Mildly Decreased	60-89	9.1%	9.0%	15.6%
	G3a	Mildly or Moderately Decreased	45-59	5.2%	9.9%	11.3%
	G3b	Moderately or Severely Decreased	30-44	3.0%	8.5%	12.7%
	G4	Severely Decreased	15-29	0.6%	1.6%	3.6%
	G5	Kidney Failure	<15	0.0%	0.0%	0.0%

KDIGO Risk Categories			
Low	Moderate	High	Very High
11.1%	16.0%	34.6%	38.3%

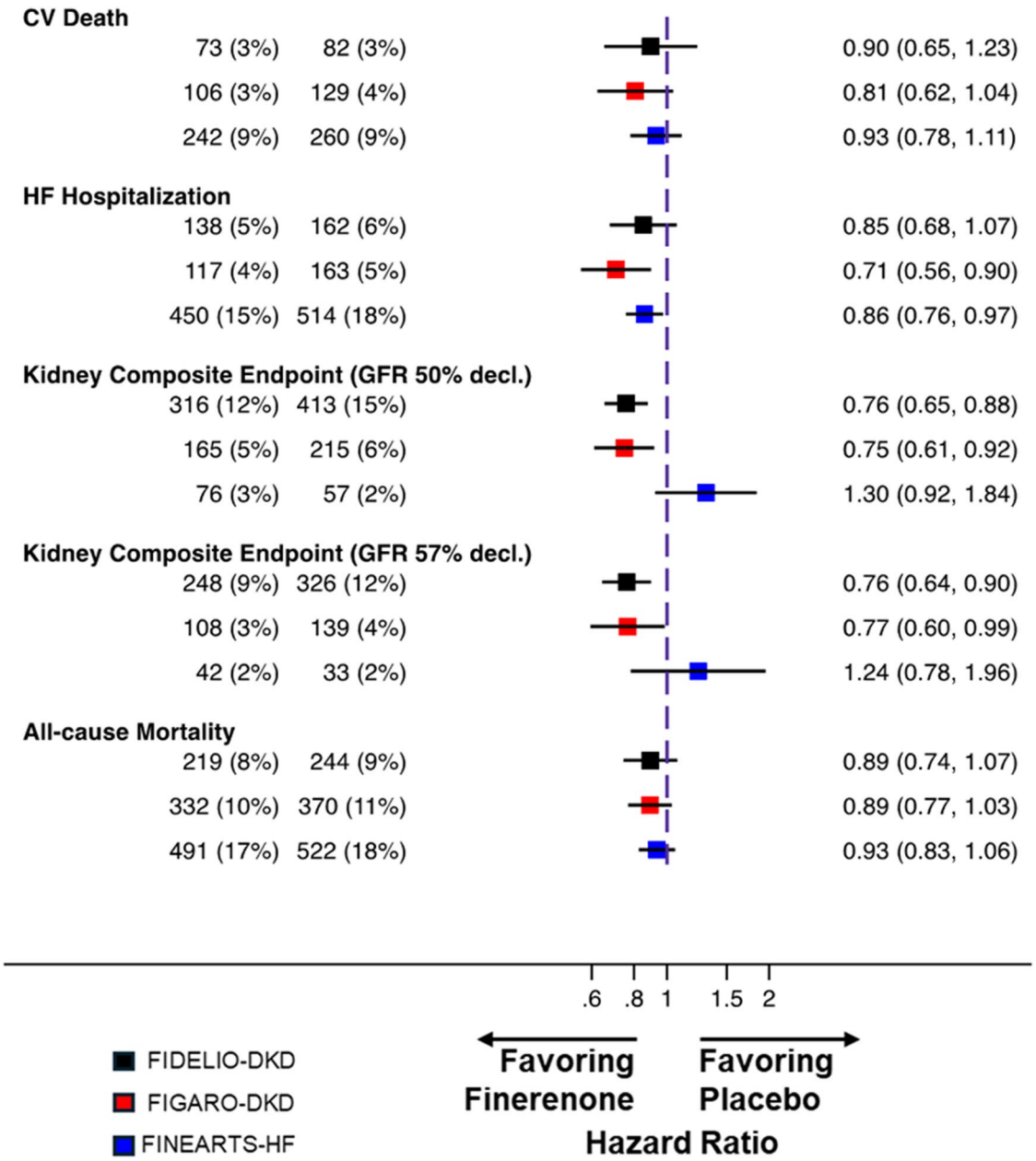
Extended Data Fig. 2 | KDIGO Risk Distribution at Baseline in FINE-HEART. Participants were at high risk for chronic kidney disease progression with either reduced estimated glomerular filtration rate or elevated levels of urine albumin creatinine ratio.

https://doi.org/10.1038/s41591-024-03264-4



Extended Data Fig. 3 | Baseline Cardio-Kidney-Metabolic Overlap in FINE-HEART. Participants included in this pooled analysis had a high degree of cardio-kidney-metabolic overlap with 90% having at least 2 conditions (heart failure, chronic kidney disease, or diabetes).

https://doi.org/10.1038/s41591-024-03264-4



Extended Data Fig. 4 | Key Efficacy Outcomes in Each Individual Trial. The bars represent 95% confidence intervals around each treatment effect point estimate.

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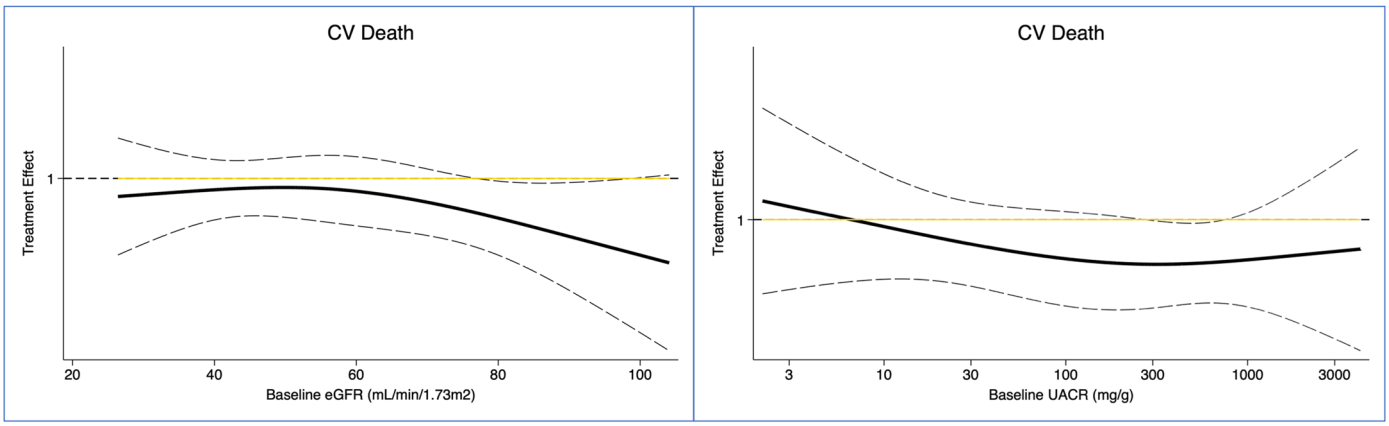

Extended Data Fig. 5 | Treatment Effect on Primary Outcome of CV Death Across Baseline eGFR (Left Panel) and UACR (Right Panel). The solid line represents the treatment effect estimate and the dashed lines represent 95% confidence intervals. Abbreviations: CV = cardiovascular; eGFR = estimated glomerular filtration rate; UACR = urine albumin creatinine ratio.

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Extended Data Table 1 | Key study design features

	FINEARTS-HF	FIDELIO-DKD and FIGARO-DKD
Validly Randomized	6,001	12,990
Countries	37	48
Patient population	HF with mildly reduced or preserved ejection fraction	CKD and T2D
Inclusion criteria	• Adults (≥40 years) • Symptomatic HF • LVEF ≥40% • Elevation natriuretic peptides • Structural heart disease • Recent diuretic use	• Adults (≥18 years old) • T2D • UACR ≥ 30 mg/g • Maximally tolerated renin-angiotensin system inhibitors
Exclusion criteria	Potassium ≤5.0 mmol/L	Potassium ≤4.8 mmol/L
Dosage and titration	eGFR ≤60: 10 up to 20 mg eGFR >60: 20 up to 40 mg (potentially down to 10 mg)	eGFR <60: 10 up to 20 mg eGFR ≥60: 20 mg (potentially down to 10 mg)
Mean daily dose	Finerenone (24.4mg) and Placebo (26.1mg)	FIDELIO-DKD: Finerenone (15.1mg) and Placebo (16.5mg) FIGARO-DKD: Finerenone (17.5mg) and Placebo (18.2mg)
Study duration	2.6 years	2.6 years (FIDELIO-DKD) 3.4 years (FIGARO-DKD)

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; T2D = type 2 diabetes; UACR = urine albumin-to-creatinine ratio

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Extended Data Table 2 | Harmonization of key outcome measures and their assessment across trials

Data Element	Harmonization Strategy
Primary Efficacy Outcome of CV Death	In the FIDELIO-DKD and FIGARO-DKD trials, deaths of undetermined causes were considered cardiovascular. In the FINEARTS-HF trial, deaths of undetermined causes were not considered cardiovascular. For the pooled FINE-HEART analysis, the primary outcome was CV death alone (excluding deaths of undetermined causes). Prespecified sensitivity analyses considered all undetermined deaths as cardiovascular in etiology.
Stratification Factors for Efficacy Models	In the time to event analyses, stratification factors were individual trial and geographic region. The countries included in each geographic region varied by trial. For the purposes of FINE-HEART, geographic region was harmonized to the following designations: • Western Europe, Oceania and Others: Australia, Austria, Belgium, Denmark, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom • Eastern Europe: Bulgaria, Czechia, Finland, Greece, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Turkey, Ukraine • Asia: China, Hong Kong, India, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, Vietnam • North America: Canada, Puerto Rico, United States of America • Latin America: Argentina, Brazil, Chile, Colombia, Mexico
Kidney Composite Outcome	The primary kidney composite Outcome specified in the FIDELITY program (which encompassed FIDELIO-DKD and FIGARO-DKD) was time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or death from kidney causes. The kidney composite outcome (a secondary outcome) in the FINEARTS-HF trial was time to first onset of kidney failure or sustained ≥50% decrease in eGFR from baseline over ≥4 weeks. Kidney outcomes were adjudicated by independent clinical events committees in each of the 3 trials. In FINE-HEART, the kidney composite outcome selected was time to first onset of kidney failure, sustained ≥50% decrease in eGFR from baseline over ≥4 weeks, or death from kidney causes.
Treatment Emergent Adverse Events	The definition of treatment emergent safety events slightly differed across trials. Whereas FINEARTS-HF considered treatment emergent adverse events as any adverse event occurring in a patient who received at least one dose of study drug and up until 3 days of permanent discontinuation, FIDELIO-DKD and FIGARO-DKD considered the same period but excluded adverse events while a participant was on temporary interruption of study drug. To remain conservative in our safety accounting, in FINE-HEART, we considered all adverse events occurring in any patient who has received at least one dose of study drug and within 3 days of permanent discontinuation, including during periods of temporary drug interruption.

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Extended Data Table 3 | Risk of bias assessment using the revised tool to assess risk of bias in randomized trials (RoB 2.0)

Study Name	Year	Randomization Bias	Intervention Deviation	Missing Outcome Data	Measurement of Outcome	Reporting of Outcome	Overall Risk
FIDELIO-DKD	2020	Low	Low	Low	Low	Low	Low
FIGARO-DKD	2021	Low	Low	Low	Low	Low	Low
FINEARTS-HF	2024	Low	Low	Low	Low	Low	Low

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Extended Data Table 4 | Baseline characteristics by trial

	FIDELIO-DKD n=5,662	FIGARO-DKD n=7,328	FINEARTS-HF n=6,001
Age	65.6 ± 9.0	64.2 ± 9.8	72.0 ± 9.6
Female	1688 (29.8%)	2244 (30.6%)	2732 (45.5%)
Race[a]			
Asian	1430 (25.3%)	1430 (19.5%)	996 (16.6%)
Black	262 (4.6 %)	258 (3.5 %)	88 (1.5 %)
Other	378 (6.7 %)	363 (5.0 %)	182 (3.0 %)
White	3592 (63.4%)	5277 (72.0%)	4735 (78.9%)
Region			
Asia	1317 (23.3%)	1323 (18.1%)	983 (16.4%)
Eastern Europe	1169 (20.6%)	2123 (29.0%)	2650 (44.2%)
Latin America	593 (10.5%)	841 (11.5%)	641 (10.7%)
North America	942 (16.6%)	1107 (15.1%)	471 (7.8 %)
Western Europe, Oceania and Others	1641 (29.0%)	1934 (26.4%)	1256 (20.9%)
Body Mass Index (kg/m^2)	31.1 ± 6.0	31.4 ± 6.0	29.9 ± 6.1
Systolic Blood Pressure (mmHg)	138.0 ± 14.4	135.7 ± 14.0	129.4 ± 15.3
Potassium (mmol/L)	4.4 ± 0.5	4.3 ± 0.4	4.4 ± 0.5
eGFR (mL/min/1.73m^2)	44.3 ± 12.6	67.8 ± 21.7	62.1 ± 19.7
eGFR Category			
< 25 mL/min/1.73m^2	135 (2.4 %)	27 (0.4 %)	32 (0.5 %)
25 to < 45 mL/min/1.73m^2	2973 (52.5%)	1251 (17.1%)	1300 (21.7%)
45 to < 60 mL/min/1.73m^2	1896 (33.5%)	1530 (20.9%)	1556 (25.9%)
≥ 60 mL/min/1.73m^2	656 (11.6%)	4519 (61.7%)	3113 (51.9%)
Baseline UACR (mg/g)	853 [446-1636]	309 [108-741]	18 [7-67]
Albuminuria Category			
A1 (< 30 mg/g)	23 (0.4 %)	207 (2.8 %)	3511 (60.6%)
A2 (30 to < 300 mg/g)	682 (12.1%)	3399 (46.4%)	1712 (29.5%)
A3 (≥300 mg/g)	4954 (87.5%)	3720 (50.8%)	574 (9.9 %)
Hemoglobin A1c (%)	7.7 ± 1.3	7.7 ± 1.4	6.4 ± 1.2
AF on Electrocardiogram	233 (4.1 %)	302 (4.1 %)	2293 (38.2%)
History of HF[b]	436 (7.7 %)	571 (7.8 %)	6001 (100.0%)
Baseline CKD[c]	5662 (100.0%)	7328 (100.0%)	2888 (48.1%)
History of DM[d]	5662 (100.0%)	7328 (100.0%)	2439 (40.6%)
Background Medication Use			
Diuretics	3209 (56.7%)	3492 (47.7%)	5930 (98.8%)
ACEi/ARB/ARNI	5648 (99.8%)	7319 (99.9%)	4759 (79.3%)
Aspirin	2787 (49.2%)	3581 (48.9%)	1948 (32.5%)
Statins	4208 (74.3%)	5179 (70.7%)	4050 (67.5%)
SGLT-2 Inhibitors	258 (4.6 %)	615 (8.4 %)	817 (13.6%)
GLP-1 Receptor Agonists	393 (6.9 %)	550 (7.5 %)	167 (2.8 %)
Potassium Lowering Therapies	136 (2.4 %)	46 (0.6 %)	13 (0.2 %)

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1 receptor agonist; SGLT-2 = sodium-glucose co-transporter-2; UACR = urine albumin-creatinine ratio

[a]Represents self reported race. Participants choosing not disclose race or who self-identified as multiple races are included in the "Other" category for descriptive purposes.

[b]HF includes all participants in FINEARTS-HF and those with investigator-reported history of HF in the primary CKD outcomes trials (FIDELIO-DKD, FIGARO-DKD)

[c]CKD includes all participants in the primary CKD outcomes trials (FIDELIO-DKD, FIGARO-DKD) and participants in FINEARTS-HF with baseline eGFR<60mL/min/1.73m^2

[d]Diabetes includes all participants in the primary CKD outcomes trials (FIDELIO-DKD, FIGARO-DKD) and those with a history of diabetes in FINEARTS-HF

[e] Includes patiromer, sodium polystyrene sulfonate, calcium polystyrene sulfonate

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Extended Data Table 5 | Components of the kidney composite endpoint

	FIGARO-DKD		FIDELIO-DKD		FINEARTS-HF		FINE-HEART (Pooled Population)		
	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Total
Kidney Composite Outcome	**165**	**215**	**316**	**413**	**76**	**57**	**557**	**685**	**1242**
Sustained decrease of eGFR ≥50% relative to baseline	152	201	267	367	73	52	492	620	1112
Sustained eGFR decline to <15ml/min/1.73m^2	28	38	164	199	25	12	217	249	466
Initiation of dialysis or kidney transplantation	32	49	117	139	7	6	156	194	350
Kidney-related death	0	2	2	2	2	2	4	6	10

Note: Participants are counted once under the composite outcome and once under each component.

Abbreviations: eGFR = estimated glomerular filtration rate

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Software and code

Policy information about availability of computer code

Data collection	Individual participant data from the 3 trials were recoded and harmonized before addition into the study dataset. Categorical variables were harmonised and all variables computed to the same scale or units of measurement. Variable names were standardized across individual trial datasets. The baseline characteristics of trial participants were extracted and relevant subgroup variables extracted. These were then combined into a dataset with an identifier for randomised treatment and the trial the data was extracted from. Time to event (harmonized to days since randomization) and censoring variables for each of the outcomes listed were also extracted. No specific additional software was used for data collection for this pooled analysis.
Data analysis	Statistical analyses were conducted using STATA version 18.

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For each of the 3 clinical trials (FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF), Bayer (the sponsor) commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel, with scope and conditions laid out as on https://vivli.org/ourmember/bayer/.

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Reporting on sex and gender	The n (%) of males/females was described overall, by randomized therapy, and by trial population (FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF). Sex was a prespecified subgroup and treatment effects on the primary endpoint were assessed separately in males and females for evidence of heterogeneity in treatment effect.
Reporting on race, ethnicity, or other socially relevant groupings	The n (%) of each racial category (White, Black, Asian, Other) was described by randomized therapy and by trial population (FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF). Race was a prespecified subgroup and treatment effects on the primary endpoint were assessed separately by racial category for evidence of heterogeneity in treatment effect.
Population characteristics	Patients with type 2 diabetes and chronic kidney disease with albuminuria (FIDELIO-DKD and FIGARO-DKD trials) and patients with heart failure with mildly reduced or preserved ejection fraction (FINEARTS-HF trial). Mean age was 67±10 years and 35.1% were women.
Recruitment	All participants randomized in each of the 3 trials were considered for this pooled analysis with only patients with critical Good Clinical Practice violations excluded.
Ethics oversight	The trial protocols were approved by ethics committees or institutional review boards at all participating sites and all patients provided explicit written informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Sample size	All participants validly randomized in each of the 3 trials (FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF) were considered for this pooled analysis. The 3 trials included 18,991 participants. All efficacy outcomes were analyzed in randomized patients under intention-to-treat principles, while all safety outcomes were analyzed in randomized patients who had taken at least one dose of the study drug.
Data exclusions	Only patients with critical Good Clinical Practice violations were excluded.
Replication	Consistency in treatment effects for the primary and most secondary endpoints was confirmed across each of the 3 individual trial populations, except for the kidney composite endpoint which appeared to be driven by effects observed in FIDELIO-DKD and FIGARO-DKD
Randomization	All participants were randomly allocated 1:1 to finerenone or placebo with initial dosing determined based on kidney function. The initial dose was 10mg for patients with an eGFR <60mL/min/1.73m2, titrated up to a target dose of 20mg once daily as tolerated. Participants with an eGFR ≥60mL/min/1.73m2 were started at the target dose of 20mg once daily. In FINEARTS-HF, participants with an eGFR >60mL/min/1.73m2 were started on 20mg and could be titrated up to 40mg once daily as tolerated, while 20 mg was the target dose for patients with eGFR ≤ 60 ml/min/1.73m2.
Blinding	All 3 trials were double-blind, placebo-controlled randomized clinical trials. Specifically, all investigators remained strictly blinded to treatment arm allocation during data collection and analysis.

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Clinical trial registration	FIDELIO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; NCT02540993]; FIGARO-DKD [Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; NCT02545049]); FINEARTS-HF [FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; NCT04435626]
Study protocol	The statistical analysis plan for this pooled analysis was prespecified and the protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42024570467).
Data collection	Participants in FIDELIO-DKD were enrolled from September 2015 through June 2018 across 48 countries. Participants in FIGARO-DKD were enrolled from September 2015 through October 2018 across 48 countries. Participants in FINEARTS-HF were enrolled from September 2020 through January 2023 across 37 countries. All 3 trials were global clinical trials with enrollment from academic/hospital-based or community health care facilities.
Outcomes	The prespecified primary endpoint for FINE-HEART was time to cardiovascular death. All deaths were adjudicated by independent clinical endpoint committees in each of the respective trials included in this pooled analysis. Other prespecified endpoints included a kidney composite endpoint (defined as a sustained decline in eGFR to ≥50% from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney causes), HF hospitalization, composite of cardiovascular death or HF hospitalization, new-onset atrial fibrillation, major adverse cardiovascular events (a composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death), all-cause death, and all-cause hospitalization. The composite of all-cause death or all-cause hospitalization was defined post hoc.

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