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ORIGINAL RESEARCH

Finerenone Reduces New-Onset Atrial Fibrillation Across the Spectrum of Cardio-Kidney-Metabolic Syndrome

The FINE-HEART Pooled Analysis

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ABSTRACT

BACKGROUND Mineralocorticoid receptor antagonists (MRA) modulate cardiac and systemic pathways such as fibrosis and inflammation, which may contribute to the onset of atrial fibrillation (AF) or atrial flutter (AFL).

OBJECTIVES In this participant-level pooled analysis of 3 large clinical trials, the authors evaluated the effect of the nonsteroidal MRA finerenone on incident AF/AFL across the cardio-kidney-metabolic (CKM) spectrum.

METHODS In this prespecified analysis, we pooled participants from 2 trials of chronic kidney disease and type 2 diabetes (FIDELIO-DKD and FIGARO-DKD) and a trial of heart failure (HF) with mildly reduced or preserved ejection fraction (FINEARTS-HF). Patients were randomized 1:1 to finerenone or placebo. New-onset AF/AFL was prospectively adjudicated in all trials by blinded clinical event committees. The risk of new-onset AF/AFL was evaluated using Cox regression models stratified by region and trial.

RESULTS Among 14,581 patients who were free of AF/AFL at trial enrollment, 631 (4.3%) experienced new-onset AF/AFL during follow-up. Predictors of new-onset AF/AFL included older age, history of HF, higher body mass index, geographic region, and higher levels of urine albumin-to-creatinine ratio. During 2.9 years of median follow-up, new-onset AF/AFL occurred in 286 (3.9%) participants receiving finerenone and 345 (4.7%) assigned to placebo (HR: 0.83; 95% CI: 0.71-0.97; $P = 0.019$). Risk reductions were consistent irrespective of number of CKM conditions ($P_{interaction} = 0.87$) and by trial ($P_{interaction} = 0.57$). Participants with new-onset AF/AFL were at significantly higher subsequent risk of cardiovascular death, HF hospitalization, and adverse kidney outcomes.

CONCLUSIONS The nonsteroidal MRA finerenone reduced the risk of new-onset AF/AFL across the CKM spectrum. (JACC. 2025;85:1649-1660) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFL = atrial flutter

CKD = chronic kidney disease

CKM = cardio-kidney-metabolic

CV = cardiovascular

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

MACE = nonfatal myocardial infarction + nonfatal stroke + HF hospitalization or CV death

MRA = mineralocorticoid receptor antagonist

UACR = urinary albumin-to-creatinine ratio

Atrial fibrillation (AF)/atrial flutter (AFL) is the most common arrhythmia and is associated with significant morbidity and mortality.[1] Cardio-kidney-metabolic (CKM) factors, independent of age and genetic predisposition, are key contributors to the risk of AF/AFL.[2] In patients with heart failure with preserved ejection fraction (HFpEF) and chronic kidney disease (CKD), AF/AFL is particularly concerning because of its association with worse cardiovascular (CV) and kidney outcomes.[3,4] These conditions often coexist within the broader context of CKM syndrome, a condition characterized by the interplay of metabolic risk factors, kidney dysfunction, and CV disease, resulting in progressive multiorgan dysfunction.[5] The significant premature morbidity and mortality associated with CKM syndrome underscores the importance of identifying therapies that provide benefits across all CKM stages and that prevent progression to late stages (such as AF/AFL).[5]

By modulating pathways involved in fibrosis and inflammation, mineralocorticoid receptor antagonists (MRAs) may influence core pathologic mechanisms underlying AF/AFL onset and progression. Recent studies have suggested that MRAs may play a role in reducing the risk of incident AF/AFL in patients with type 2 diabetes and CKD.[6] However, the role of MRAs in mitigating the risk of AF/AFL in patients within the broader CKM syndrome remains unexplored. Finerenone, a nonsteroidal MRA, has previously demonstrated efficacy in preventing or delaying adverse CV and kidney outcomes in CKM syndrome.[7] In this prespecified FINE-HEART analysis across 3 large phase 3 trials, we investigated the effects of finerenone on the risk of new-onset AF/AFL in patients across the CKM spectrum.

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METHODS

DESIGN OF THE FINE-HEART POOLED ANALYSIS. FINE-HEART (CRD42024570467) was a prospectively planned and registered participant-level pooled analysis of 2 trials of CKD and type 2 diabetes (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 heart failure (HF) patients with mildly reduced or preserved ejection fraction with and without diabetes (FINEARTS-HF [FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; NCT04435626]). The details of the study design, inclusion/exclusion criteria, and primary results of each of the 3 trials have been previously published.[8-10] The protocols were approved by local ethics committees at each site, and independent monitoring committees oversaw the trials.

Briefly, FIDELIO-DKD studied the efficacy and safety of finerenone compared with placebo in 5,674 patients with CKD and type 2 diabetes, all receiving background therapy with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Patients with CKD were eligible if they had an estimated glomerular filtration rate (eGFR) of 25 to 60 mL/min/1.73 m^2 of body surface area, moderately elevated albuminuria with a urinary albumin-to-creatinine ratio (UACR) of 30 to 300 mg/g, and diabetic retinopathy. Alternatively, patients with severe albuminuria (UACR 300-5,000 mg/g) were eligible if their eGFR was 25 to 75 mL/min/1.73 m^2.

FIGARO-DKD assessed the efficacy and safety of finerenone vs placebo in 7,437 patients with CKD and type 2 diabetes on background therapy with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Eligible patients included those with an eGFR of 25 to 90 mL/min/1.73 m^2 and moderately elevated albuminuria, defined as UACR of 30 to 300 mg/g or severe albuminuria (300-5,000 mg/g) with an eGFR of at least 60 mL/min/1.73 m^2. For both trials, serum potassium was required to be ≤4.8 mmol/L at screening.

FINEARTS-HF investigated the efficacy and safety of finerenone in adults aged ≥40 years with symptomatic heart failure with NYHA functional class II-IV functional limitations, a left ventricular ejection fraction of ≥40%, diuretic requirement at least 30 days before randomization, structural heart

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disease (left atrial enlargement or left ventricular hypertrophy), and elevated natriuretic peptide levels.

Individual participant-level data were accessed and pooled with harmonized data elements for baseline characteristics and clinical outcomes in the prospectively planned and registered FINE-HEART analysis. A total of 196 participants were excluded from FINE-HEART, including 60 patients in FIDELIO-DKD, 85 patients in FIGARO-DKD, and 15 patients in FINEARTS-HF who were excluded before database lock from all analyses because of critical violations of good clinical practice or because of re-randomization of the same subject. The remaining 36 participants excluded (from FIDELIO-DKD and FIGARO-DKD) were excluded because of critical violations of good clinical practice after database lock. For this analysis, participants who reported a history of AF/AFL or had evidence of AF/AFL in baseline electrocardiogram were excluded (n = 4,410). After these exclusions, the final pooled sample size was 14,581 participants without AF/AFL at baseline.

ADJUDICATION OF NEW-ONSET AF/AFL. Patients with previously documented history of AF/AFL or presence of AF/AFL on baseline electrocardiogram (ECG) at randomization were not considered for subsequent new-onset AF/AFL events. The primary outcome for this study was new-onset AF/AFL, which was a prespecified secondary outcome in FINE-HEART and was prospectively adjudicated in all 3 trials by a blinded independent clinical endpoint committee. New onset AF/AFL required electrocardiographic confirmation on 12-lead electrocardiogram, electrophysiology study, telemetry, or short-term rhythm monitoring. New-onset AF was defined by absence of P waves and the presence of an irregular heart rate and rhythm on electrocardiogram or electrophysiology telemetry. New-onset AFL was defined as presence of sawtooth flutter waves, a regular and rapid atrial rate of 250 to 350 per minute, and a regular or irregular ventricular rate, depending on the level of atrioventricular conduction (eg, 2:1 or 3:1). New-onset AF/AFL could be paroxysmal, persistent, or permanent and did not require specific treatments (such as initiation of rate/rhythm control therapy or anticoagulation) and did not require hospitalization to meet the criteria for adjudication. Only the first new-onset episode of AF/AFL was considered. New-onset AF/AFL was analyzed under the intention-to-treat principles.

OTHER CLINICAL OUTCOMES. The risk of CV and kidney outcomes after a first episode of new-onset AF/AFL was additionally evaluated. Key outcomes included CV death (excluding undetermined causes of death), HF hospitalization, major adverse CV events (MACE, a composite of nonfatal myocardial infarction, nonfatal stroke, HF hospitalization or CV death), kidney composite endpoint (defined as a sustained decrease in eGFR to ≥50% from baseline, sustained decline in eGFR to <15 mL/min/1.73 m^2, kidney failure, and death due to kidney failure), and all-cause death.

STATISTICAL ANALYSES. Baseline characteristics were described using counts and percentages for categorical variables, mean ± SD for normally distributed continuous variables, and median (Q1-Q3) for non-normally distributed continuous variables. We compared baseline characteristics between treatment arms using standardized mean differences. For descriptive purposes, we additionally compared baseline characteristics between those who did and did not experience new-onset AF/AFL during follow-up.

New-onset AF/AFL by treatment arm was analyzed using Cox proportional hazards model stratified by geographic region and trial. No data were missing for outcomes or stratification variables, as all new-onset AF/AFL outcomes were adjudicated and both region and trial had complete data. There was a violation of the proportional hazards assumption for the main model examining the effects of finerenone on new-onset AF/AFL development. As such, a sensitivity analysis was completed using a restricted mean time lost model, a nonparametric survival analysis method that does not rely on such assumptions. To address any concerns about competing risks, an additional sensitivity analysis was conducted to evaluate risk of new-onset AF/AFL with all-cause mortality as a competing event using a Fine-Gray subdistribution hazard model. The association between new-onset AF/AFL and subsequent risk of clinical outcomes (CV death, HF hospitalization, MACE, kidney composite endpoint, and all-cause death) was assessed using time-updated Cox proportional hazards models, in which participants contributed person-time to the non-AF/AFL group until the time of AF/AFL onset, after which they were classified in the AF/AFL group. Models were stratified by region and trial and further adjusted for age, body mass index, estimated glomerular filtration rate (eGFR), UACR, history of HF, history of diabetes, and treatment arm. The selection of covariates for adjustment was guided by both clinical relevance and statistically significant differences detected when comparing baseline characteristics at $P < 0.05$. Predictors of new-onset AF/AFL were assessed using multivariable Cox models using a stepwise forward selection, adding variables with a $P < 0.05$. Statistical analyses were performed using STATA version 18.

TABLE 1 Baseline Characteristics by Treatment Arm Among FINE-HEART Participants Without AF/AFL at Baseline

	Placebo (n = 7,314)	Finerenone (n = 7,267)	Standardized Mean Differences
Age, y	65.4 ± 10.0	65.2 ± 9.7	0.02
Female	2,390 (32.7)	2,487 (34.2)	−0.03
Race			−0.01
Asian	1,648 (22.5)	1,595 (21.9)	
Black	282 (3.9)	275 (3.8)	
Other	395 (5.4)	419 (5.8)	
White	4,989 (68.2)	4,978 (68.5)	
Region			0.008
Asia	1,524 (20.8)	1,499 (20.6)	
Eastern Europe	2,063 (28.2)	2,103 (28.9)	
Latin America	904 (12.4)	896 (12.3)	
North America	1,035 (14.2)	1,016 (14.0)	
Western Europe, Oceania, and Others	1,788 (24.4)	1,753 (24.1)	
Baseline body mass index, kg/m^2	30.9 ± 6.0	30.9 ± 6.0	0.0006
Baseline systolic blood pressure, mm Hg	135.59 ± 14.56	135.72 ± 14.51	−0.01
Baseline potassium, mmol/L	4.37 ± 0.45	4.37 ± 0.44	0.006
Baseline eGFR, mL/min/1.73 m^2	59.50 ± 21.98	59.23 ± 21.71	0.01
eGFR group			−0.002
<25 mL/min/1.73 m^2	79 (1.1)	78 (1.1)	
25-<45 mL/min/1.73 m^2	2,169 (29.7)	2,139 (29.4)	
45-<60 mL/min/1.73 m^2	1,849 (25.3)	1,856 (25.5)	
≥60 mL/min/1.73 m^2	3,216 (44.0)	3,193 (43.9)	
Baseline UACR, mg/g	399 (91-1,014)	401 (89-1,002)	0.003
Baseline albuminuria (mg/g) category			0.006
A1 (<30 mg/g)	953 (13.1)	949 (13.1)	
A2 (30-<300 mg/g)	2,152 (29.6)	2,163 (29.9)	
A3 (≥300 mg/g)	4,169 (57.3)	4,116 (56.9)	
Baseline hemoglobin A_{1C}, %	7.5 ± 1.4	7.5 ± 1.4	−0.02
History of HF	1,784 (24.4)	1,724 (23.7)	0.02
Baseline CKD	6,496 (88.8)	6,482 (89.2)	−0.01
History of diabetes	6,558 (89.7)	6,539 (90.0)	−0.01
Diuretic use at baseline	4,368 (59.7)	4,249 (58.5)	0.03
ACEI/ARB/ARNI	7,079 (96.8)	7,038 (96.8)	−0.004
Aspirin	3,814 (52.1)	3,802 (52.3)	−0.004
Statins	5,339 (73.0)	5,201 (71.6)	0.03
SGLT2 inhibitors	594 (8.1)	581 (8.0)	0.005
GLP-1 receptor agonists	443 (6.1)	491 (6.8)	−0.03
Potassium-lowering therapy	85 (1.2)	92 (1.3)	−0.01

Values are mean ± SD, n (%), or median (Q1-Q3).

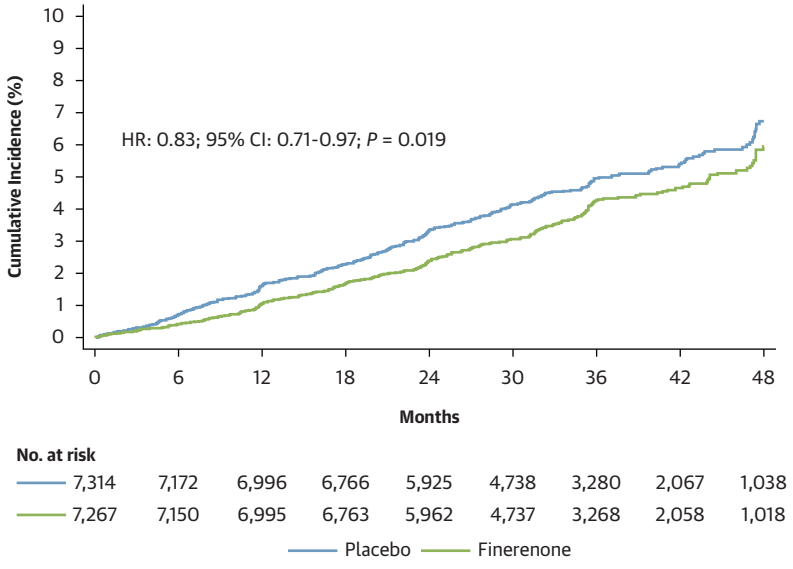
A1 = normal to mildly increased; A2 = moderately increased; A3 = severely increased based on KDIGO classification; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor/neprilysin inhibitor; CKD = chronic kidney disease; eGFR = glomerular filtration rate; GLP = glucagon-like peptide; HF = heart failure; SGLT2 = sodium-glucose cotransporter 2; UACR = urine albumin-to-creatinine ratio.

RESULTS

BASELINE CHARACTERISTICS. A total of 14,581 participants across the 3 trials without a history of AF/AFL and who did not have AF/AFL present on baseline ECG were included in this study. A total of 7,267 participants were randomized to finerenone and 7,314 to placebo. Baseline characteristics were well balanced between treatment arms (finerenone vs placebo) (**Table 1**). Among participants without AF/AFL at baseline, 631 patients (4.3%) experienced new-onset AF/AFL during follow-up. The baseline characteristics of participants among those who did and did not experience new-onset AF/AFL during follow-up are shown in Supplemental Table 1.

EFFECT OF FINERENONE ON NEW-ONSET AF/AFL. During 2.9 years of median follow-up, 286 (3.9%) of the participants receiving finerenone and 345 (4.7%) assigned to placebo experienced new-onset AF/AFL. The incidence of AF/AFL was significantly lower for participants treated with finerenone as compared to placebo (1.4 vs 1.6 per 100 patient-years, HR: 0.83; 95% CI: 0.71, 0.97; P = 0.019) (**Figure 1**).

FIGURE 1 New-Onset AF/AFL in FINE-HEART Participants by Treatment Arm



There was a violation of the proportional hazards assumption for the main model examining the effects of finerenone on new-onset development of atrial fibrillation (AF)/atrial flutter (AFL). As such, a sensitivity analysis was completed using a restricted mean time lost model (RMTL) (a nonparametric survival analysis method), which was consistent with these findings (RMTL ratio: 0.79; 95% CI: 0.67-0.93; $P = 0.004$).

The cumulative risk was 6.7% and 5.9% in the placebo and finerenone arm, respectively. The number-needed-to-treat at 4 years follow-up was 126. Similar findings were observed when using restricted mean time lost model, a nonparametric survival analysis model (ratio: 0.79; 95% CI: 0.67-0.93; $P = 0.004$) and when treating all-cause mortality as a competing event (subhazard ratio: 0.83; 95% CI: 0.71-0.97; $P = 0.020$). Risk reductions were consistent irrespective of number of CKM conditions (HF, CKD, diabetes; $P_{interaction} = 0.87$) and by trial ($P_{interaction} = 0.57$). The treatment effect of finerenone was generally consistent across other major subgroups; however, Asian participants appeared to derive greater benefit, while Black participants appeared to experience higher event rates with finerenone (with wide confidence limits around these estimates in light of few events in this racial subgroup) ($P_{interaction}$ for race = 0.004) (Figure 2). In a sensitivity analysis, all subgroup findings were also consistent after competing risks analysis (Supplemental Table 2).

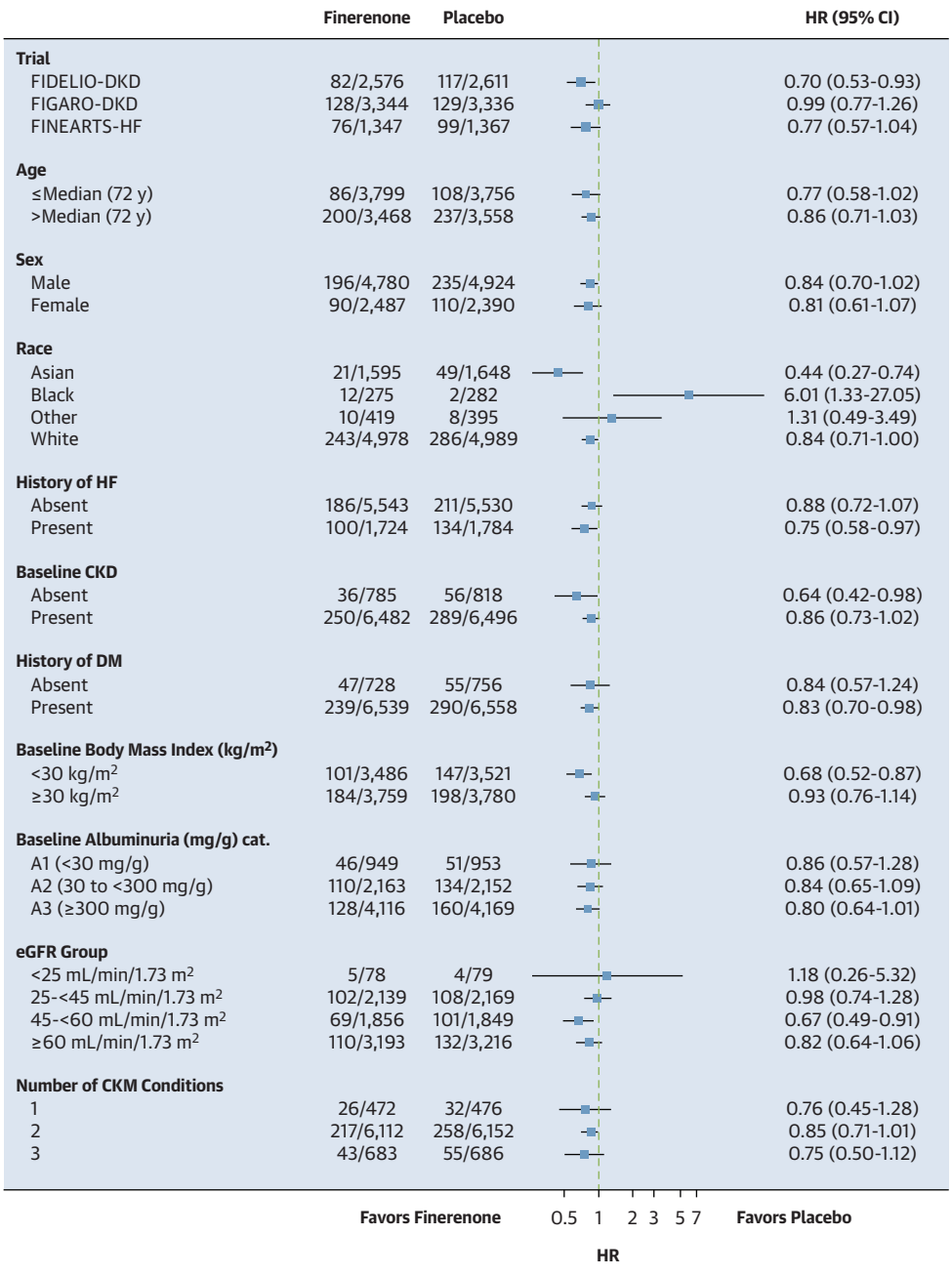
PREDICTORS OF NEW-ONSET AF/AFL. Independent baseline clinical characteristics associated with new-onset AF/AFL included older age, history of HF, higher body mass index, geographic region, and higher UACR. Conversely, female sex and treatment with finerenone were associated with lower rates of new-onset AF/AFL (Table 2).

NEW-ONSET AF/AFL STATUS AND SUBSEQUENT CV AND KIDNEY RISK. In time-varying models, participants who experience new-onset AF/AFL during follow-up had a higher subsequent risk for HF hospitalization or CV death (adjusted HR: 3.7; 95% CI: 2.9-4.6; $P < 0.001$) (Figure 3), MACE (adjusted HR: 2.8; 95% CI: 2.2-3.5; $P < 0.001$), kidney composite outcome (adjusted HR: 2.0; 95% CI: 1.4-2.7; $P < 0.001$), and all-cause death (adjusted HR: 4.3; 95% CI: 3.6-5.2; $P < 0.001$) during follow-up (Table 3).

DISCUSSION

In this prespecified analysis of FINE-HEART, the nonsteroidal MRA finerenone significantly reduced the risk of incident AF/AFL among participants across 3 contemporary CKM trials. The effect size was clinically meaningful and consistent across most major clinical subgroups, including those with increasing CKM overlap/burden. Importantly, participants who experience new-onset AF/AFL were at a substantially higher subsequent risk of adverse CV and kidney outcomes than were those who remained free of AF/AFL during follow-up (Central Illustration). These findings highlight the

FIGURE 2 Treatment Effects of Finerenone on New-Onset AF/AFL Across Major Clinical Subgroups in the FINEHEART Pooled Analysis



AF = atrial fibrillation; AFL = atrial flutter; cat. = category; CKD = chronic kidney disease; CKM conditions = cardio-kidney metabolic conditions; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FIDELIO-DKD = Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD = Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; FINEARTS-HF = FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; HF = heart failure.

role of finerenone in reducing the risk of new-onset AF/AFL, mitigating downstream complications, and ultimately improving outcomes in patients across the CKM spectrum.

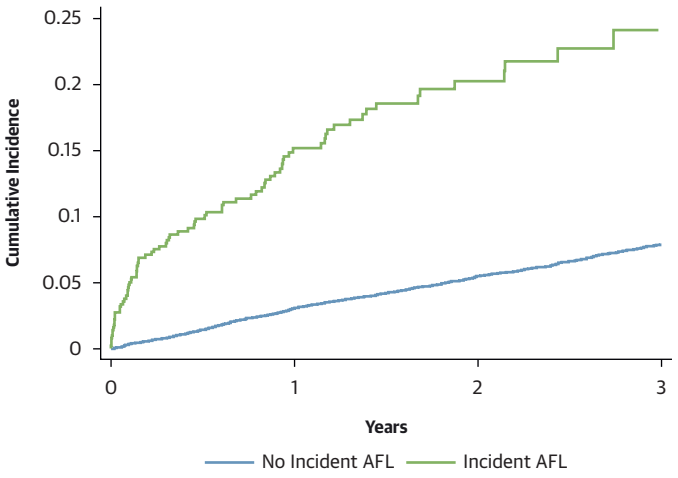
The beneficial effect of finerenone in reducing the risk of incident AF/AFL aligns with the results of prior studies demonstrating a reduction in new-onset AF/AFL with MRAs.[11-13] Notably, the EMPHASIS-HF

TABLE 2 Independent Predictors of New-Onset AF/AFL in the FINE-HEART Pooled Analysis

	HR (95% CI)	z Statistic	*P* Value
Age (per 10 y)	1.80 (1.62-1.99)	10.97	<0.001
History of heart failure	2.46 (2.03-2.99)	9.06	<0.001
BMI (per 5 kg/m^2)	1.24 (1.16-1.33)	6.01	<0.001
Region			
Asia	Reference		
Eastern Europe	1.55 (1.15-2.08)	2.89	0.004
Latin America	0.97 (0.65-1.45)	0.13	0.90
North America	1.47 (1.06-2.05)	2.30	0.022
Western Europe, Oceania, others	1.94 (1.45-2.58)	4.49	<0.001
UACR (per doubling)	1.07 (1.03-1.10)	3.55	<0.001
Female	0.78 (0.65-0.93)	2.80	0.005
Treatment with finerenone	0.83 (0.71-0.97)	2.30	0.022

BMI = body mass index; UACR = urine albumin-to-creatinine ratio.

FIGURE 3 New-Onset AF/AFL and Subsequent Risk of Heart Failure Hospitalization or Cardiovascular Death



Green line represents failure function for time from incident atrial fibrillation (AF)/atrial flutter (AFL). Blue line represents time from randomization.

(Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) trial demonstrated a 40% reduction in AF/AFL risk with eplerenone in patients with heart failure with reduced ejection fraction, whereas the FIDELIO-DKD trial showed a 30% reduction with finerenone in patients with type 2 diabetes and CKD.[6,14] By contrast, the TOPCAT (Treatment of Cardiac Function with an Aldosterone Antagonist) trial, which evaluated spironolactone in HFpEF, did not show a reduction in AF/AFL incidence.[15] Differences in trial design and patient populations may account for this discrepancy, together with the lack of prospective adjudication of new-onset AF/AFL in TOPCAT, which may have led to less precision in its assessment.

The observed racial differences in treatment response are of unclear significance and require further study. Prior trials of MRAs in CKM disease states have generally demonstrated consistent benefits across racial groups.[10,16,17] In our analysis, self-described Asian patients appeared to derive greater benefit from finerenone in reducing new-onset AF/AFL. Notably, a recent meta-analysis showed greater reductions in UACR and systolic blood pressure in Asian patients with CKD treated with MRAs.[18] Conversely, self-described Black patients experienced a higher risk of AF/AFL with finerenone, which should be interpreted with caution in light of the small sample size and limited number of events in this racial subgroup, suggesting that the observed effect may be spurious. This also contrasts with most previous trials, where Black patients generally showed similar CV and kidney benefits with MRA therapy. However, RALES (Randomized Aldactone Evaluation Study) suggested potentially lesser efficacy of spironolactone in Black patients with heart failure with reduced ejection fraction.[19] These findings highlight the need for future studies to confirm potential racial differences in treatment response, and they underscore the importance of improving Black representation in clinical trials.

AF/AFL is intricately linked with CKM syndrome through shared pathophysiology mechanisms, and incident and prevalent AF/AFL are considered CKM stage 4.[20,21] Consistent with prior evidence, HF, obesity, and higher UACR—all key components of CKM syndrome—were significant predictors of new-onset AF/AFL.[2,22,23] These predictors highlight the complex interplay of systemic factors in AF/AFL development, many of which are modulated by mineralocorticoid receptor signaling. Reassuringly, we observed that the benefits of finerenone in reducing new-onset AF/AFL were consistent across the spectrum of CKM burden.

The mechanisms underlying the observed beneficial effects of MRAs on AF/AFL risk may involve inhibition of proarrhythmic and profibrotic pathways mediated by MR signaling. Patients with AF/AFL exhibit increased MR expression in the atria compared with those in normal sinus rhythm.[24] Animal models have demonstrated that aldosterone promotes a proarrhythmic state by increasing T-type calcium currents and sarcoplasmic reticulum calcium load, which drives arrhythmogenesis.[24] Additionally,

TABLE 3 New-Onset AF/AFL and Subsequent Risk of Cardiovascular, Kidney, and Mortality Outcomes in Time-Updated Models in the FINEHEART Pooled Analysis

	No AF/AFL (n = 13,950)	New-Onset AF/AFL (n = 631)[a]	*P* Value
Heart failure hospitalization or cardiovascular death	1,100 events (2.7 per 100 patient-y) (Ref)	81 events (12.4 per 100 patient-y) HR: 3.65 (95% CI: 2.88-4.62)	<0.001
Cardiovascular death	448 events (1.1 per 100 patient-y) Ref	58 events (7.3 per 100 patient-y) HR: 5.49 (95% CI: 4.11-7.33)	<0.001
Heart failure hospitalization	729 events (1.7 per 100 patient-y) (Ref)	57 events (8.7 per 100 patient-y) HR: 3.80 (95% CI: 2.87-5.03)	<0.001
Major adverse cardiovascular event	1,735 events (4.3 per 100 patient-y) (Ref)	83 events (14.5 per 100 patient-y) HR: 2.81 (95% CI: 2.24-3.53)	<0.001
Kidney composite outcome	1,064 events (2.8 per 100 patient yrs) (Ref)	41 events (6.4 per 100 patient yrs) HR: 1.98 (95% CI: 1.44-2.73)	<0.001
All-cause death	1,234 events (2.9 per 100 patient-y) (Ref)	134 events (16.9 per 100 patient-y) HR: 4.31 (95% CI: 3.58-5.19)	<0.001

[a]HRs adjusted for age, region, body mass index, estimated glomerular filtration rate, urine albumin-to-creatinine ratio, history of heart failure and diabetes, and treatment arm.
AF = atrial fibrillation; AFL = atrial flutter; FINEHEART = FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; Ref = reference.

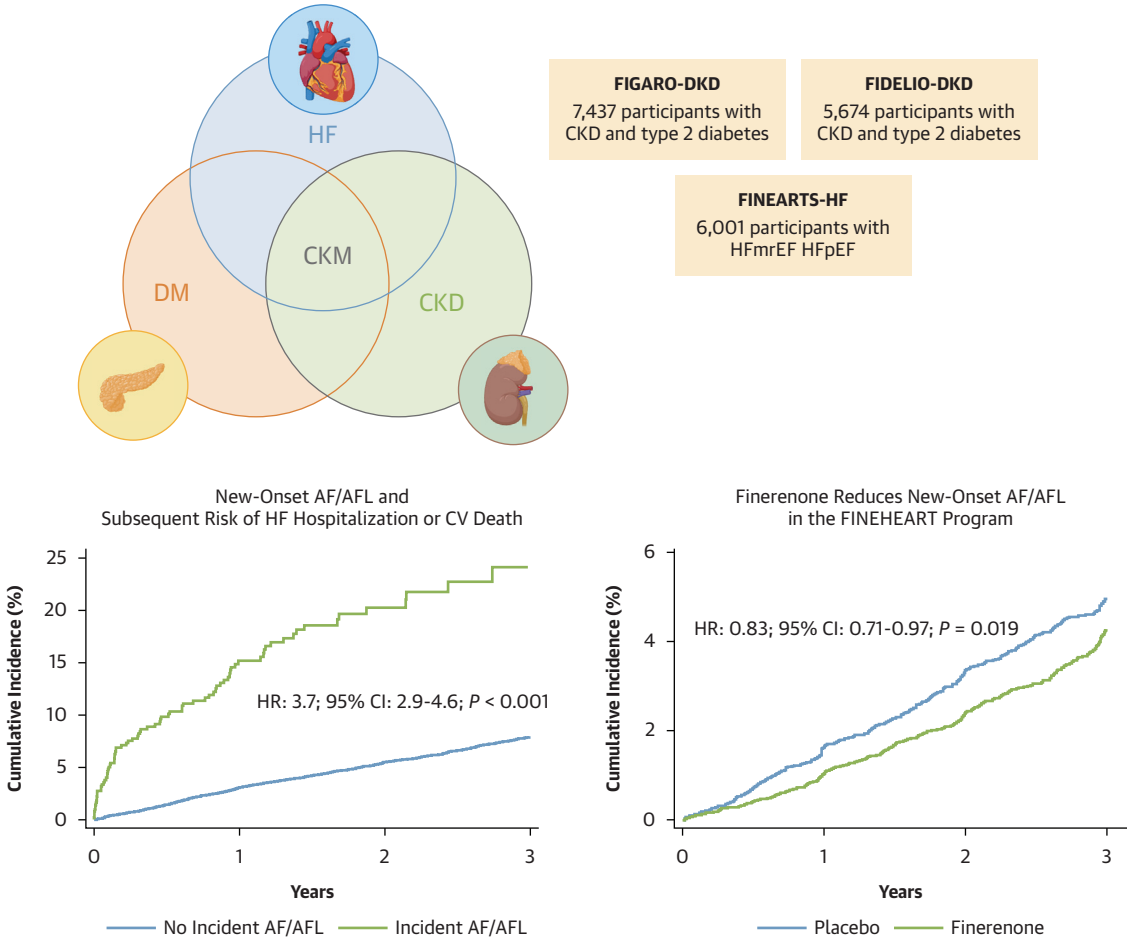
aldosterone induces oxidative stress and inflammation in the atrial myocardium, facilitating AF/AFL inducibility.[25-29] MR activation further amplifies these processes by upregulating profibrotic genes, activating nuclear factor κB, and increasing matrix metalloproteinase-2 activity, mediated by NADPH oxidase 2.[30] Collectively, these effects are effectively attenuated by MRAs, highlighting their potential to mitigate AF/AFL risk through suppression of atrial remodeling and electrical instability.

Consistent with prior studies, participants who experience new-onset AF/AFL during follow-up had a significantly higher subsequent risk of adverse CV and kidney outcomes. The occurrence of AF/AFL is associated with increased morbidity and mortality in patients with CKD[4] and HF, irrespective of left ventricular ejection fraction.[31] Although these findings highlight the potential impact of new-onset AF/AFL on CV and kidney risk, causality cannot be inferred. AF/AFL may serve as a marker of worsening overall health rather than as a direct contributor to these outcomes.

STUDY LIMITATIONS. First, our findings are derived from randomized clinical trials, which may not be representative of the general population. Additionally, the data combine trials with distinct designs, inclusion criteria, and primary endpoints, potentially introducing variability in the observed effects and limiting direct comparisons across subgroups. However, we did not observe significant heterogeneity in the effects of finerenone on new-onset AF/AFL across the 3 trials. The study population also lacked sufficient representation from certain groups, such as women and Black patients, which may restrict the applicability of our findings to underrepresented populations with differing AF/AFL risk profiles. In addition, <10% of participants were on sodium-glucose cotransporter 2 inhibitors or incretin-based therapies, treatments potentially associated with reduced AF/AFL risk, limiting the ability to evaluate additive effects of finerenone.[32,33] Also, residual confounding cannot be excluded, given that unmeasured factors such as physical activity levels, dietary patterns (including alcohol intake), and socioeconomic status may influence both AF/AFL risk and treatment response.

Furthermore, whereas new-onset AF/AFL was rigorously adjudicated based on electrocardiographic confirmation, the absence of systematic protocolized rhythm monitoring may have led to underestimation of paroxysmal AF/AFL, particularly among asymptomatic individuals. AF/AFL episodes were captured through clinically indicated ECGs, telemetry, and short-term rhythm monitoring; continuous or extended ambulatory monitoring was not part of the trial protocols, so that transient events may have potentially been missed. Whereas the relative risk reduction was meaningful, on an absolute scale this was relatively modest, with a number-needed-to-

CENTRAL ILLUSTRATION **Finerenone and New-Onset AF/AFL FINE-HEART**



Incident AF/AFL was associated with significantly worse adverse CV outcomes in this high risk CKM population. The nonsteroidal MRA finerenone reduced the risk of new-onset AF/AFL across the CKM spectrum.

Pabon MA, et al. JACC. 2025;85(17):1649-1660.

AF = atrial fibrillation; AFL = atrial flutter; CKD = chronic kidney disease; CKM = cardio-kidney metabolic syndrome; CV = cardiovascular; DKD = diabetic kidney disease; DM = diabetes mellitus; FIDELIO-DKD = Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD = Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; FINEARTS-HF = FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; HF = heart failure; HFmEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid receptor antagonist.

treat >100. We believe that this is likely related to undercapturing of events, leading to underestimation of the true absolute risk reduction. Finally, our analysis focused on new-onset AF/AFL, and we did not assess the effect of finerenone on AF/AFL recurrence in patients with a history of AF/AFL but no AF/AFL at baseline. Future studies should investigate whether finerenone influences recurrent AF/AFL (including measures of AF/AFL burden) in this population.

CONCLUSIONS

This FINEHEART pooled analysis demonstrated that finerenone significantly reduced the risk of new-onset AF/AFL. Given the heightened risk of AF/AFL in CKM syndrome, finerenone may be an important therapeutic option to help reduce AF/AFL -related morbidity and improve outcomes across the CKM spectrum.

DATA SHARING STATEMENT. For each of the 3 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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The trials included in this pooled analysis were funded by Bayer AG. The trial steering committees designed and oversaw their conduct in collaboration with the sponsor. However, the primary analyses, interpretation of the data, and manuscript drafting were conducted independently by the academic teams. Dr Pabon has received support from the American Heart Association (AHA 24CDA1272604) and the Doris Duke Foundation (DDCF 2023-0212) and reports no conflicts of interest. Dr Filippatos has received lecture fees from Bayer, Boehringer Ingelheim, Servier, and Novartis; has received trial committee membership fees from Bayer, Boehringer Ingelheim, Servier, Impulse Dynamics, Vifor, and Medtronic; has received consulting fees from Cardior and Novo Nordisk; and has received research grants from the European Union. Dr Claggett 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. Dr Desai has received institutional research grants from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer; and has received personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River 2 Renal, Roche, Veristat, Verily, and Zydus. Dr Jhund has received speaker fees from AstraZeneca and ProAdWise Communications; has received advisory board fees from AstraZeneca; has received research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, and Roche Diagnostics; his employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk; and he is the Director GCTP Ltd. Dr Brinker is a full-time employee of Bayer AG. Dr Schloemer is a full-time employee of Bayer AG; and is a co-inventor of finerenone, and holds U.S. and European patents relating to finerenone (US8436180B2 and EP2132206B1). Dr Hofmeister is a full-time employee of Bayer AG. Dr Li is a full-time employee of Bayer AG. Dr Lam has received research support from Novo Nordisk 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. Dr Senni has served on advisory boards for and has received consultancy fees and honoraria from Novartis, Abbott, Merck, Merck Sharp & Dohme, Vifor, AstraZeneca, Cardurion, Novo Nordisk, Bayer, and Boehringer Ingelheim. 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Dr Anker has received grants and personal fees from Vifor and Abbott Laboratories; and has received personal fees for consultancies, trial committee work and/or lectures from Actimed, AstraZeneca, Bayer, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, Impulse Dynamics, Lilly, Mankind Pharma, Medtronic, Novartis, Novo Nordisk, Occlutech, Pfizer, Regeneron, Relaxera, Repairon, Scirent, Sensible Medical, Vectorious, Vivus, and V-Wave; named co-inventor of 2 patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents. Dr Pitt has served as a consultant for Bayer, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lexicon, Anacardia, and G3 Pharmaceuticals; and has served as a consultant for and received stock options or stocks from Sea Star Medical, Vifor, scPharmaceuticals, SQinnovations, KBP Biosciences, Sarfez, Cereno Scientific, Prointel, and Brainstorm Medical; and holds a U.S. patent (9931412: Site-specific delivery of eplerenone to the myocardium) and has a U.S.patent pending (63/045,783: Histone modulating agents for the prevention and treatment of organ damage). Dr Agarwal has received support from Bayer; has received royalties or licenses from UpToDate; has received consulting fees from Boehringer Ingelheim, Novartis, Akebia, Intercept Pharma, and Alnylam; has received support for meetings from Boehringer Ingelheim, Novartis, Akebia, and Vertex; and has participated on DSMBs or advisory boards for Vertex, Eloxx, and Chinook. 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Chemicals & Pharmaceuticals, Lupin Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications,

Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group and Translational Medicine Academy; has served on the DSMB for WIRB-Copernicus Group Clinical; and he is also a director of Global Clinical Trial Partners, Ltd. Dr Solomon has received research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GlaxoSmithKline, Ionis, Eli Lilly, MyoKardia, NIH/NHLBI, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Eli Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. Dr Vaduganathan has received research grant support, has served on advisory boards for, 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 Amgen, AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardio-kidney-metabolic, finerenone, heart failure, mineralocorticoid receptor antagonist

APPENDIX For supplemental tables, please see the online version of this paper.