Cardiorenal Protection with Nonsteroidal Mineralocorticoid Receptor Antagonism: An In-Depth Evaluation of the FIDELIO-DKD Trial

Pharmacophysiological Rationale and Trial Design

Chronic kidney disease complicating type 2 diabetes represents a substantial and expanding cardiorenal challenge globally, acting as a primary driver of end-stage kidney disease and dramatically compounding cardiovascular mortality.[1] Chronic overactivation of the mineralocorticoid receptor has been identified as a critical pathophysiologic pathway that promotes progressive tissue inflammation, oxidative stress, and subsequent fibrosis within both the renal parenchymal and cardiovascular structures.[4] Although traditional steroidal mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, effectively suppress mineralocorticoid receptor-mediated damage, their systemic clinical application in patients with impaired kidney function has been severely restricted by an unacceptably high risk of severe hyperkalemia and off-target endocrine side effects like gynecomastia.[7]

Finerenone is a novel, selective, nonsteroidal mineralocorticoid receptor antagonist characterized by a bulky, nonsteroidal structure that facilitates a highly specific and tight binding configuration within the mineralocorticoid receptor ligand-binding domain.[1] This unique chemical profile prevents the recruitment of transcriptional coactivators as effectively as steroidal antagonists but with a significantly lower propensity to induce hyperkalemia or exhibit cross-reactivity with androgen, progesterone, estrogen, or glucocorticoid receptors.[1] The landmark phase 3 trial, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease, was designed to test whether the addition of finerenone to standard-of-care renin-angiotensin system blockade would safely delay chronic kidney disease progression and reduce cardiovascular events in patients with type 2 diabetes and advanced nephropathy.[3]

To satisfy eligibility for randomization in the trial, patients were required to be at least 18 years of age, have a clinical diagnosis of type 2 diabetes, and be maintained on optimized, maximally tolerated labeled doses of a single renin-angiotensin system inhibitor, such as an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, which had been adjusted prior to screening.[3] Patients were stratified into two primary clinical cohorts based on their baseline estimated glomerular filtration rate and urinary albumin-to-creatinine ratio [7]:

- **Moderately Elevated Albuminuria Cohort:** Patients with a urinary albumin-to-creatinine ratio ranging from $30 \text{ to } < 300 \text{ mg/g}$, accompanied by an estimated glomerular filtration rate of $25 \text{ to } < 60 \text{ mL/min/1.73 m}^2$ and a documented history of

diabetic retinopathy.[7]

- **Severely Elevated Albuminuria Cohort:** Patients with a urinary albumin-to-creatinine ratio ranging from $300 \text{ to } 5000 \text{ mg/g}$, accompanied by an estimated glomerular filtration rate of $25 \text{ to } < 75 \text{ mL/min/1.73 m}^2$.[7]

Additionally, candidates were required to exhibit a stable baseline serum potassium level of $\leq 4.8 \text{ mmol/L}$ at the time of screening to ensure a safe safety margin for initiating mineralocorticoid receptor blockade.[7] Exclusion criteria included chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association class II through IV), uncontrolled hypertension, other known non-diabetic kidney diseases, or a recent cardiovascular event.[7]

A total of 13,911 patients were screened, of whom 5,674 underwent randomized allocation in a 1:1 ratio to receive either oral finerenone ($N = 2833$) or matching placebo ($N = 2841$).[3] The initial daily dosage of the study drug was determined based on the estimated glomerular filtration rate measured at the screening visit: patients with an estimated glomerular filtration rate of $25 \text{ to } < 60 \text{ mL/min/1.73 m}^2$ received 10 mg once daily, while those with an estimated glomerular filtration rate $\geq 60 \text{ mL/min/1.73 m}^2$ initiated therapy at 20 mg once daily.[7] Uptitration to the target daily dose of 20 mg was strongly encouraged after one month of therapy, provided the estimated glomerular filtration rate remained stable and serum potassium concentrations did not exceed 4.8 mmol/L.[4]

At baseline, the randomized cohort was characterized by a mean age of 66 years, a female representation of 30%, a mean estimated glomerular filtration rate of $44.3 \text{ mL/min/1.73 m}^2$ (with approximately 55% of patients presenting with an estimated glomerular filtration rate $< 45 \text{ mL/min/1.73 m}^2$), and a median urinary albumin-to-creatinine ratio of 852 mg/g.[7] At the trial conclusion, after a median follow-up of 2.6 years, the mean daily dose of the active treatment was 15.1 mg in the finerenone group and the sham-adjusted daily dose was 16.5 mg in the placebo group.[3] Background cardiorenal and glucose-lowering medications were highly representative of clinical practice during the study period.[3]

Clinical Parameter or Baseline Medication	Finerenone Group (N=2833)	Placebo Group (N=2841)

Mean Age (years) [7]	66.0	66.0
Female Sex, n (%) [7]	850 (30.0%)	852 (30.0%)
Mean Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73 m²) [7]	44.4	44.3
Distribution of eGFR by Subcategory [19]:		
-- $<$ mL/min/1.73 m², n (%)	71 (2.5%)	65 (2.3%)
-- 25 to $<$ mL/min/1.73 m², n (%)	1480 (52.2%)	1495 (52.6%)
-- 45 to $<$ mL/min/1.73 m², n (%)	940 (33.2%)	955 (33.6%)
-- $\geq$ mL/min/1.73 m², n (%)	340 (12.0%)	315 (11.1%)
Median Urinary Albumin-to-Creatinine Ratio (UACR, mg/g) [7]	852.0	852.0
Mean Glycated Hemoglobin (HbA1c, %) [7]	7.7	7.7
Mean Systolic Blood Pressure (mmHg) [7]	138.0	138.0
Baseline Renin-Angiotensin System Blockade (ACEi or ARB), n (%) [3]	2833 (100.0%)	2841 (100.0%)
-- Angiotensin-Converting Enzyme Inhibitor (ACEi), n	958 (33.8%)	978 (34.4%)

(%) [19]		
-- Angiotensin Receptor Blocker (ARB), n (%) [19]	1875 (66.2%)	1863 (65.6%)
Baseline SGLT2 Inhibitor Use, n (%) [17]	120 (4.2%)	139 (4.9%)
Baseline GLP-1 Receptor Agonist Use, n (%) [22]	195 (6.9%)	195 (6.9%)

Primary Kidney Composite Outcome: Absolute Risk Reductions and Actuarial Projections

The primary composite endpoint of the trial, evaluated in a rigorous time-to-event intention-to-treat analysis, was a kidney-specific composite comprised of the time to first occurrence of [3]:

1. Kidney failure, clinically defined as end-stage kidney disease (manifested as the initiation of chronic dialysis for at least 90 days or kidney transplantation) or a sustained estimated glomerular filtration rate of $< 15\ \mathrm{mL/min/1.73\ m^2}$.[4]
2. A sustained decrease from baseline of at least 40% in the estimated glomerular filtration rate, with both the glomerular filtration rate drop and the transition to $< 15\ \mathrm{mL/min/1.73\ m^2}$ requiring confirmation via a second consecutive central laboratory measurement performed at least 4 weeks after the initial index measurement.[3]
3. Death from renal causes.[3]

During the median follow-up of 2.6 years, a primary composite outcome event occurred in 504 of 2,833 patients (17.8%) in the active finerenone arm, compared to 600 of 2,841 patients (21.1%) in the placebo arm.[3] This risk reduction was highly statistically significant, demonstrating an 18% relative risk reduction with finerenone compared to placebo (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; $P = 0.001$ or $P = 0.0014$).[3]

The absolute clinical impact of these primary findings can be quantified through two distinct analytical frameworks: the crude trial-duration absolute risk reduction and the actuarial Kaplan-Meier life-table projection.[8]

The crude absolute risk reduction represents the simple mathematical difference in cumulative raw event rates between the two randomized cohorts across the entire trial duration [8]:

$$\text{Crude ARR} = \text{Placebo Event Rate} - \text{Finerenone Event Rate}$$

$$\text{Crude ARR} = 21.12\% - 17.79\% = 3.33\%$$

This risk difference of 3.3% indicates that for every 100 patients treated with finerenone rather than placebo, approximately 3.3 primary composite kidney events were prevented over the median 2.6-year follow-up period.[8] The crude trial-duration Number Needed to Treat (NNT) to prevent a single primary kidney event is derived directly as the reciprocal of the crude risk difference [25]:

$$\text{Crude NNT} \approx \frac{1}{0.0333} \approx 30 \quad (\text{calculated as } 30.03)$$ [25]

To account for variable patient follow-up and censoring over time, investigators utilized actuarial Kaplan-Meier methods to project absolute clinical benefits at specific chronological intervals.[4] At the 3-year (36-month) treatment landmark, the cumulative actuarial absolute risk reduction widened to [26]:

$$\text{Actuarial ARR (3 years)} = 3.4\% \quad (95\%\ \text{CI}, 0.6\% \text{ to } 6.2\%) \quad [26, 27]$$

This actuarial risk difference yields a 3-year actuarial NNT of [3]:

$$\text{NNT (3 years)} = 29 \quad (95\%\ \text{CI}, 16 \text{ to } 166) \quad [3, 26, 27, 28]$$

A specific, prespecified high-risk temporal cohort analysis of the trial database illustrates the progression of cumulative incidence and actuarial risk differences for both the primary kidney composite and the secondary cardiovascular composite over a 4-year follow-up period, demonstrating how the cardiorenal benefits of finerenone expand as treatment duration extends [29]:

Follow-Up Duration	Finerenone Cumulative Incidence (%)	Placebo Cumulative Incidence (%)	Actuarial Risk Difference (%) (95% CI)	Actuarial NNT (95% CI)
Primary Kidney Composite [29]:				

-- 1 Year	2.1% (95% CI, 1.1 to 3.9)	4.5% (95% CI, 2.9 to 6.8)	-2.0% (95% CI, -5.0 to 0.0)	41 (95% CI, 21 to 3349)
-- 2 Years	10.1% (95% CI, 7.3 to 13.3)	15.2% (95% CI, 11.9 to 18.9)	-5.0% (95% CI, -10.0 to -1.0)	19 (95% CI, 10 to 187)
-- 3 Years	25.4% (95% CI, 20.6 to 30.6)	23.0% (95% CI, 18.6 to 27.6)	3.0% (95% CI, -4.0 to 9.0)	-40 (Actuarial Shift)
-- 4 Years	34.9% (95% CI, 28.2 to 41.8)	30.0% (95% CI, 24.0 to 36.2)	5.0% (95% CI, -4.0 to 14.0)	-20 (Actuarial Shift)
Secondary CV Composite [29]:				
-- 1 Year	4.6% (95% CI, 2.9 to 6.8)	8.0% (95% CI, 5.7 to 10.7)	-3.0% (95% CI, -7.0 to -0.2)	29 (95% CI, 15 to 434)
-- 2 Years	11.2% (95% CI, 8.4 to 14.4)	14.7% (95% CI, 11.5 to 18.2)	-4.0% (95% CI, -8.0 to 1.0)	29 (Temporal Hold)
-- 3 Years	17.5% (95% CI, 13.6 to 21.7)	20.7% (95% CI, 16.7 to 24.9)	-3.0% (95% CI, -9.0 to 3.0)	31 (Temporal Hold)
-- 4 Years	25.0% (95% CI, 19.4 to 30.9)	29.1% (95% CI, 22.3 to 36.2)	-4.0% (95% CI, -13.0 to 5.0)	24 (95% CI, 12 to 150)

To understand the pathophysiologic mechanism of finerenone, the primary composite kidney outcome must be deconstructed into its individual components to determine which clinical parameters drove the overall risk reduction.[9] This component-level deconstruction in the intention-to-treat population indicates that the overall renal benefit was driven by the preservation of glomerular filtration capacity [9]:

- **Sustained decrease in eGFR of $\geq 40\%$:** This functional surrogate was the principal

driver of the primary endpoint, occurring in 16.9% ($n = 479$) of the finerenone cohort compared to 20.3% ($n = 577$) of the placebo cohort, translating to a statistically significant 19% hazard reduction (HR, 0.81; 95% CI, 0.72 to 0.92; crude absolute risk reduction of 3.4%).[9]

- **Kidney Failure:** Clinical events occurred in 7.3% ($n = 208$) of the finerenone group versus 8.3% ($n = 235$) of the placebo group, demonstrating a favorable trend but falling short of statistical significance during the 2.6-year trial follow-up (HR, 0.87; 95% CI, 0.72 to 1.05; crude absolute risk reduction of 1.0%).[7]
- **End-Stage Kidney Disease (ESKD):** Chronic dialysis or kidney transplantation occurred in 4.2% ($n = 120$) of finerenone-treated patients versus 4.9% ($n = 139$) of placebo-treated patients (HR, 0.86; 95% CI, 0.67 to 1.10; crude absolute risk reduction of 0.7%).[7]
- **Sustained Decrease in eGFR to < 15 mL/min/1.73 m²:** Developed in 5.9% ($n = 166$) of the finerenone group versus 7.0% ($n = 198$) of the placebo group (HR, 0.82; 95% CI, 0.67 to 1.01; crude absolute risk reduction of 1.1%).[30]
- **Death from Renal Causes:** Renal deaths were rare in both groups during the follow-up period, occurring in less than 0.1% ($n = 2$) of patients in the finerenone arm and less than 0.1% ($n = 2$) in the placebo arm.[9]

Key Secondary Cardiovascular Efficacy Outcomes and Subgroup Interactions

Chronic kidney disease is associated with a high burden of cardiovascular disease, and patients are far more likely to experience cardiovascular death or heart failure hospitalization than to survive to reach end-stage kidney failure.[5] To evaluate the systemic impact of mineralocorticoid receptor antagonism, the first secondary outcome tested in the hierarchical structure of the trial was a composite cardiovascular endpoint consisting of the time to first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.[3]

Over the 2.6-year median follow-up period, a secondary composite cardiovascular event occurred in 13.0% (367 of 2,833) of patients receiving finerenone, compared to 14.8% (420 of 2,841) of patients receiving placebo.[3] This difference represents a statistically significant 14% hazard reduction in favor of finerenone (HR, 0.86; 95% CI, 0.75 to 0.99; $P = 0.03$).[3] The corresponding crude absolute risk reduction was 1.8%, yielding a crude trial-duration NNT of approximately 56.[8] Actuarial life-table projection at the 3-year (36-month) landmark estimated an absolute risk reduction of 2.4% (95% CI, 0.3% to 4.5%), which corresponds to an actuarial NNT

of 42 (95% CI, 22 to 397) to prevent one cardiovascular death, myocardial infarction, stroke, or heart failure hospitalization.[27]
A deconstructed analysis of individual components of this secondary composite cardiovascular endpoint demonstrates that the absolute benefit was primarily driven by reductions in hospitalizations for heart failure and cardiovascular death [7]:

- **Hospitalization for Heart Failure:** Occurred in 4.9% ($n = 139$) of the finerenone group versus 5.7% ($n = 162$) of the placebo group, demonstrating a 14% hazard reduction (HR, 0.86; 95% CI, 0.68 to 1.08; crude absolute risk reduction of 0.8%).[7]
- **Cardiovascular Death:** Developed in 4.5% ($n = 128$) of the finerenone group versus 5.3% ($n = 150$) of the placebo group (HR, 0.86; 95% CI, 0.68 to 1.08; crude absolute risk reduction of 0.8%).[7]
- **Nonfatal Myocardial Infarction:** Occurred in 2.5% ($n = 70$) of the finerenone group versus 3.1% ($n = 87$) of the placebo group, showing a 20% hazard reduction (HR, 0.80; 95% CI, 0.58 to 1.09; crude absolute risk reduction of 0.6%).[7]
- **Nonfatal Stroke:** Developed in 3.2% ($n = 90$) of the finerenone group versus 3.1% ($n = 87$) of the placebo group, showing no relative benefit (HR, 1.03; 95% CI, 0.76 to 1.38).[7]

To determine whether baseline cardiovascular disease altered the efficacy of finerenone, investigators performed a prespecified subgroup analysis stratifying patients by a history of atherosclerotic cardiovascular disease (ASCVD), which was present in approximately 46% of the trial population.[5] Finerenone demonstrated highly consistent cardiorenal protection across both subgroups [7]:

Clinical Outcome by Baseline ASCVD Status	**Finerenone Group (N=2833)**	**Placebo Group (N=2841)**	**Hazard Ratio (95% CI)**	**P-Value for Interaction**
Primary Kidney Composite Outcome [7]:				
-- Patients with baseline	17.2%	20.1%	0.82 (	$P_{\text{interaction}} =$

ASCVD			$0.73–0.93$)	
-- Patients without baseline ASCVD	8.9%	9.7%	0.82 ($0.73–0.93$)	
CV Death or Heart Failure Hospitalization [7]:				
-- Patients with baseline ASCVD	11.5%	13.9%	0.82 ($0.68–0.98$)	$P_{\text{interaction}} =$
-- Patients without baseline ASCVD	5.6%	6.4%	0.85 ($0.68–1.05$)	
Composite Kidney Outcome [7]:				
-- Patients with baseline ASCVD	4.7%	6.4%	0.71 ($0.55–0.92$)	$P_{\text{interaction}} =$
-- Patients without baseline ASCVD	6.2%	7.8%	0.78 ($0.63–0.96$)	

Advanced Subpopulation Analyses: Asian, Chinese, and Frailty Cohorts

To ensure these primary findings apply broadly across diverse patient demographics, investigators conducted prespecified subpopulation analyses, which revealed several notable cardiorenal protection trends.[12]

The Asian subpopulation ($n = 2894$), representing approximately 22% of the combined phase 3 database, showed a particularly pronounced response to finerenone therapy.[32] In the Asian cohort, the hard composite kidney endpoint—defined as a sustained $\geq 57\%$ decrease in estimated glomerular filtration rate, kidney failure, or renal death—occurred in 7.4% ($105/1412$) of the finerenone group compared to 11.8% ($170/1446$) of the placebo group.[32] This represents a statistically significant 36% relative risk reduction (HR, 0.64; 95% CI, 0.50 to 0.82), which was more pronounced than the 15% reduction observed in the non-Asian subpopulation (HR, 0.85; 95% CI, 0.71 to 1.00; $P_{\text{interaction}} = 0.0493$).[32]

Similarly, for the standard $\geq 40\%$ estimated glomerular filtration rate decline primary composite kidney outcome, Asian patients treated with finerenone experienced a cumulative event rate of 15.4% ($217/1412$) compared to 22.0% ($318/1446$) for those receiving placebo, translating to a highly significant 33% relative risk reduction (HR, 0.67; 95% CI, 0.56 to 0.80).[32] In contrast, the non-Asian subpopulation showed a more modest treatment effect on the $\geq 40\%$ kidney composite (HR, 0.93; 95% CI, 0.84 to 1.04; $P_{\text{interaction}} = 0.0009$).[32] Despite these regional differences in estimated glomerular filtration rate decline, short-term reduction in albuminuria at Month 4 was highly consistent between the groups: finerenone reduced the urinary albumin-to-creatinine ratio by 33% in Asians and by 32% in non-Asians compared to placebo.[32]

Within this regional cohort, investigators evaluated a prespecified subgroup of 372 Chinese participants (finerenone $n = 188$, placebo $n = 184$) managed across 67 centers in China.[12] In this Chinese cohort, finerenone therapy was associated with a 41% relative risk reduction for the primary composite kidney outcome compared to placebo (HR, 0.59; 95% CI, 0.39 to 0.88; $P = 0.009$).[36] Based on an absolute between-group difference of 12.2% after 30 months, the NNT to prevent one primary kidney composite outcome event was only 8 (95% CI, 4 to 84).[1]

Parameter (Chinese Subpopulation Analysis)	Finerenone Cohort (N=188)	Placebo Cohort (N=184)
Mean Age (years) [35]	59.85	60.68
Male Sex, n (%) [35]	145 (77.1%)	145 (78.8%)
Mean Duration of Type 2	13.31	14.17

Diabetes (years) [35]		
Mean Glycated Hemoglobin (HbA1c, %) [35]	7.47	7.44
Mean Systolic Blood Pressure (mmHg) [35]	135.83	132.89
Mean Estimated Glomerular Filtration Rate (mL/min/1.73 m²) [35]	45.88	45.25
Baseline Urinary Albumin-to-Creatinine Ratio (median, mg/g) [35]	1326.61	1210.41
Mean Baseline Serum Potassium (mmol/L) [35]	4.29	4.28
Concomitant ARB Use at Baseline, n (%) [35]	167 (88.8%)	161 (87.5%)
Concomitant ACEi Use at Baseline, n (%) [35]	21 (11.2%)	23 (12.5%)
Any Treatment-Emergent Adverse Event (TEAE), n (%) [35]	176 (93.6%)	179 (97.3%)
Any Serious Adverse Event (SAE), n (%) [35]	111 (59.0%)	113 (61.4%)
Any Hyperkalemia-related TEAE, n (%) [35]	70 (37.2%)	47 (25.5%)
-- Serious Hyperkalemia TEAE, n (%) [35]	4 (2.1%)	1 (0.5%)
-- Hyperkalemia leading to trial discontinuation, n (%) [1]	8 (4.3%)	2 (1.1%)
Comparable Acute Kidney	3 (1.6%)	3 (1.6%)

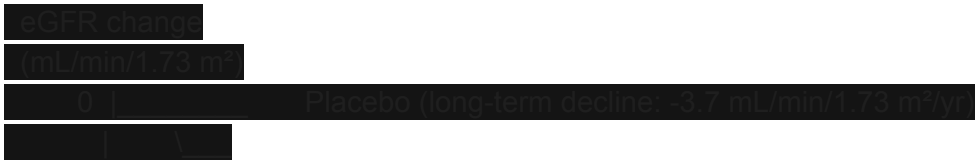
Injury (AKI) Rate, n (%) [1]		

To determine whether patient vulnerability affected the safety or efficacy of finerenone, investigators conducted a post hoc analysis stratifying participants by baseline frailty.[33] Frailty was quantified using a 30-item Frailty Index constructed using the Rockwood cumulative deficit approach, which includes baseline laboratory measures, clinical history, and physical indicators.[33]

Finerenone demonstrated consistent cardiorenal protection across all frailty subgroups.[37] The active treatment reduced the primary composite kidney outcome and secondary cardiovascular outcome to a similar degree in both frail and non-frail patients, with no significant interaction between baseline frailty status and treatment effect ($P_{\text{interaction}} = 0.93$ for the kidney composite, $P_{\text{interaction}} = 0.35$ for the cardiovascular composite).[37] Additionally, finerenone significantly reduced the urinary albumin-to-creatinine ratio and slowed estimated glomerular filtration rate decline compared to placebo across all frailty strata.[37] While serious adverse events and hyperkalemia increased with higher baseline frailty in both treatment arms, the relative safety profile of finerenone remained favorable, indicating that advanced age or clinical frailty should not preclude its use in patients with chronic kidney disease and type 2 diabetes.[33]

Kinetic eGFR Slope and Long-term Kidney Protection

An in-depth analysis of estimated glomerular filtration rate trends over time reveals a distinct, dual-phase renal hemodynamic and parenchymal protection response to finerenone therapy.[18] During the initial phase of therapy (from baseline to Month 4), finerenone was associated with a temporary, hemodynamic "dip" in estimated glomerular filtration rate.[18] The least-squares mean change in estimated glomerular filtration rate from baseline to Month 4 was $-3.3\ \text{mL/min/1.73 m}^2$ in the finerenone group compared to $-1.0\ \text{mL/min/1.73 m}^2$ in the placebo group.[18] This treatment-induced difference of $-2.38\ \text{mL/min/1.73 m}^2$ (95% CI, -2.77 to -1.98; $P < 0.0001$) reflects a reduction in intraglomerular pressure, a reversible hemodynamic effect similar to that observed with sodium-glucose cotransporter 2 inhibitors or renin-angiotensin system blockers.[18]



Following this initial hemodynamic adjustment, finerenone demonstrated sustained, long-term renal parenchymal protection.[18] From Month 4 through the end of follow-up, the annualized rate of estimated glomerular filtration rate decline was significantly slower in finerenone-treated patients than in those receiving placebo.[38] The least-squares mean eGFR slope was $-2.5\ \mathrm{mL/min/1.73\ m^2/year}$ in the finerenone arm compared to $-3.7\ \mathrm{mL/min/1.73\ m^2/year}$ in the placebo arm, demonstrating that finerenone slows the long-term deterioration of kidney function.[38]

This preservation of kidney function is further illustrated by the long-term estimated glomerular filtration rate treatment differences.[18] The transient estimated glomerular filtration rate deficit observed with finerenone at Month 4 was gradually reversed, with the estimated glomerular filtration rate curves crossing within 2 years of initiating therapy.[18] By Month 36, finerenone-treated patients showed a statistically significant estimated glomerular filtration rate advantage of $+0.98\ \mathrm{mL/min/1.73\ m^2}$ (95% CI, 0.17 to 1.78; $P = 0.0172$) compared to placebo.[39] At Month 44, this protection widened further to $+1.98\ \mathrm{mL/min/1.73\ m^2}$ (95% CI, 0.83 to 3.13; $P = 0.0008$), confirming sustained kidney protection.[39]

Safety, Hyperkalemia Management, and Modern Combination Therapies

The primary therapeutic trade-off of mineralocorticoid receptor antagonism in patients with chronic kidney disease is the potential for potassium retention in the distal nephron, which must be balanced against the drug's long-term cardiorenal benefits.[8] Finerenone was associated with a higher rate of investigator-reported hyperkalemia compared to placebo, occurring in 18.3% of finerenone-treated patients versus 9.0% of those receiving placebo (an absolute risk increase of 9.3%).[9]

Analyzing serum potassium concentrations using standard central laboratory thresholds provides a more objective safety assessment [8]:

- **Mild Hyperkalemia ($\geq 5.5\ \mathrm{mmol/L}$):** Finerenone therapy increased the risk of mild potassium elevation compared to placebo.[8]

- **Moderate to Severe Hyperkalemia ($\geq 6.0\ \text{mmol/L}$):** Finerenone was associated with a lower incidence of severe potassium elevations than typically observed with traditional steroidal antagonists, though the risk remained higher than with placebo.[8]

To mitigate hyperkalemia risks, the trial utilized a strict potassium management protocol, which included a baseline serum potassium threshold of $\leq 4.8\ \text{mmol/L}$ at screening, temporary treatment suspension if potassium levels exceeded $5.5\ \text{mmol/L}$, and restarting therapy at $10\ \text{mg}$ once daily only after potassium concentrations fell to $\leq 5.0\ \text{mmol/L}$.[4] Under this protocol, the rate of permanent drug discontinuation due to hyperkalemia was low, though higher with finerenone than placebo (2.3% vs. 0.9%; absolute risk difference of 1.4%).[3] Importantly, no hyperkalemia-related deaths were reported in either group.[5]

The clinical impact of continuing versus discontinuing therapy is illustrated by the primary outcome event rates.[41] During the active treatment period, crude event rates for the composite kidney outcome were lower in the finerenone group than in the placebo group (1.09 vs. 1.71 events per 100 patient-years).[41] In contrast, following premature treatment discontinuation, event rates rose dramatically in both groups (11.95 vs. 13.67 events per 100 patient-years), demonstrating that sustained adherence to finerenone is necessary to maintain its cardiorenal benefits.[41]

Hyperkalemia risk and treatment discontinuation rates were closely related to baseline estimated glomerular filtration rate.[38] Among patients with a baseline estimated glomerular filtration rate $< 60\ \text{mL/min/1.73 m}^2$, the rate of permanent discontinuation due to hyperkalemia was 2.4% in the finerenone group versus 0.8% in the placebo group.[38] In contrast, for patients with a baseline estimated glomerular filtration rate $\geq 60\ \text{mL/min/1.73 m}^2$, the rate of hyperkalemia-related discontinuation was lower and more comparable between groups (0.6% in the finerenone group versus 0.3% in the placebo group).[38]

To optimize safety in clinical practice, combining finerenone with a sodium-glucose cotransporter 2 (SGLT2) inhibitor represents a highly effective therapeutic strategy.[17] SGLT2 inhibitors promote renal potassium excretion through osmotic diuresis and kaliuresis, which mathematically counters the potassium-retaining effect of mineralocorticoid receptor blockade.[17] While baseline use of SGLT2 inhibitors in FIDELIO-DKD was low (4.6%), a prespecified subgroup analysis showed that the rate of hyperkalemia-related adverse events with finerenone was halved in patients using SGLT2 inhibitors at baseline compared to those who were not (8.1% vs. 18.7%).[17]

Furthermore, actuarial projections of triple combination therapy—combining an SGLT2 inhibitor, a GLP-1 receptor agonist, and a nonsteroidal mineralocorticoid receptor antagonist—in patients with type 2 diabetes and moderately to severely elevated albuminuria estimate a 3-year absolute risk reduction of 4.4% (95% CI, 3.0% to 5.7%) for the primary composite kidney

outcome.[43] This triple-therapy combination is projected to reduce the 3-year NNT to 23 (95% CI, 18 to 33), representing a major advance in cardiorenal protection.[43]

Methodological Nuances and Regulatory Updates

To maintain scientific accuracy, clinical evaluations of the FIDELIO-DKD data must incorporate recent regulatory revisions.[44] In 2023, a clinical research audit identified a Good Clinical Practice violation by a Site Management Organization at Japanese Site 20003, which affected the trial's database.[44]

In response, regulatory bodies, including the European Medicines Agency, retrospectively updated their product summaries to exclude data from impacted participants.[44] This resulted in the retrospective exclusion of 36 participants in the clinical trials—specifically, 34 Japanese participants and 2 other participants who had been flagged for potential prospective violations after the initial 2020 data release.[44] These retrospective adjustments resulted in minor numerical corrections in the product labeling approved in 2025, which coincided with the introduction of a new 40 mg strength for heart failure indications.[44]

The retrospective participant exclusions did not alter the statistical significance or clinical conclusions of the FIDELIO-DKD trial, and the original primary analysis of 5,674 randomized patients remains the standard scientific reference for the clinical community.[3] Finerenone remains a fundamentally secure, guidelines-recommended foundation of contemporary therapy for slowing chronic kidney disease progression and reducing cardiovascular risk in adults with type 2 diabetes and diabetic nephropathy.[2]

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