Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes

Rajiv Agarwal


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Global burden of kidney failure – diabetes is the leading cause

- 7600 million – global population
- 844 million – global prevalence of CKD
- 3.9 million – patients on KRT
- As many might die due to lack of KRT

CKD, chronic kidney disease
FIDELIO-DKD rationale
High residual risk of CKD progression with current therapies

Hemodynamic\(^1,^2\)
(elevated blood pressure and/or intraglomerular pressure)

**RENAAL\(^3\)**
Composite primary endpoint*

*Composite of doubling of serum creatinine, ESKD or death
FIDELIO-DKD rationale
High residual risk of CKD progression with current therapies

*Composite of kidney failure, doubling of serum creatinine, or renal or CV death

**Metabolic**
(elevated blood pressure and/or intraglomerular pressure)

**Hemodynamic**
(poor glycemic control)

**CREDENCE**
Cardiorenal composite endpoint*

Placebo + ACEi/ARB
Canagliflozin + ACEi/ARB

HR=0.70 (95% CI 0.59–0.82); p=0.00001

Patients with an event (%)

Residual risk

Months since randomization

0 6 12 18 24 30 36 42
0 5 10 15 20 25
FIDELIO-DKD rationale
High residual risk of CKD progression with current therapies

Hemodynamic$^{1,2}$
(elevated blood pressure and/or intraglomerular pressure)

Metabolic$^{1,2}$
(poor glycemic control)

Inflammation and fibrosis$^{1-3}$

Not specifically targeted by existing treatments$^{1,4}$

FIDELIO-DKD rationale

Finerenone is a novel, selective, non-steroidal MRA that inhibits inflammation and fibrosis and protects against progressive kidney and CV dysfunction in preclinical models¹.

ARTS-DN (patients with CKD and T2D) – finerenone improved albuminuria independent of measured changes in BP².

**Hypothesis:** MR antagonism with finerenone slows CKD progression and reduces CV morbidity and mortality in patients with advanced CKD and T2D³.

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FIDELIO-DKD eligibility criteria

### Key inclusion criteria
- Aged ≥18 years with CKD and T2D
- Pretreated with optimized therapy, including an ACEi or ARB at a max tolerated dose for ≥4 weeks
- Serum potassium ≤4.8 mmol/L
- Diabetic retinopathy for patients with A2 albuminuria

### Albuminuria categories (mg albumin/g creatinine)

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²)</th>
<th>A1 Normal to mildly elevated</th>
<th>A2 Moderately elevated</th>
<th>A3 Severely elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 &gt;90</td>
<td>0–29</td>
<td>30–299</td>
<td>≥300–4999</td>
</tr>
<tr>
<td>G2 60–89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a 45–59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b 30–44</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>G4 15–29</td>
<td></td>
<td></td>
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<tr>
<td>G5 &lt;15</td>
<td></td>
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</tr>
</tbody>
</table>

### Key exclusion criteria
- Non-diabetic kidney disease, including clinically relevant renal artery stenosis
- HFrEF with NYHA class II–IV
- HbA1c >12%
- Uncontrolled arterial hypertension

*Mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit
FIDELIO-DKD study design

13,911 patients enrolled

Run-in (4–16 weeks) → Screening

5734 patients randomized

Placebo → Finerenone 10 or 20 mg od*

Post-treatment follow-up

2.6 years’ median follow-up

Hierarchical endpoints

1. Kidney composite
   Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death

2. CV composite
   Time to CV death, non-fatal MI, non-fatal stroke or hospitalization for HF

3. Death from any cause
4. Hospitalization for any cause
5. Change in UACR
6. Second kidney composite

*10 mg if screening eGFR <60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m², uptitration encouraged from month 1 if serum potassium ≤4.8 mEq/L and eGFR stable. eGFR, estimated glomerular filtration rate; HF, heart failure;
Patients were randomized from 48 countries worldwide

- Europe (n=2358; 41.6%)
- Asia (n=1579, 27.8%)
- Oceania (n=101, 1.8%)
- North America (n=944; 16.6%)
- Latin America (n=593; 10.5%)
- Africa (n=99, 1.7%)

5734 patients randomized – 5674 patients in FAS – 99.7% completed the study
# Baseline demographics and medications

<table>
<thead>
<tr>
<th></th>
<th>Finerenone (n=2833)</th>
<th>Placebo (n=2841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Male, %</td>
<td>69%</td>
<td>71%</td>
</tr>
<tr>
<td>Mean duration of T2D, years</td>
<td>16.6</td>
<td>16.6</td>
</tr>
<tr>
<td>Mean HbA1c, %</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>138/76</td>
<td>138/76</td>
</tr>
<tr>
<td>Mean serum [K+], mmol/L</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>ACEis, %</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>ARBs, %</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Glucose-lowering therapies, %</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td><strong>Insulin and analogs</strong></td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>GLP-1RAs</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>SGLT-2is</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor
Baseline kidney labs – balanced between treatment groups

Mean eGFR 44

- eGFR <45: 54.9%
- eGFR 45–<60: 33.5%
- eGFR ≥60: 11.6%

Median UACR ~850

- UACR ≥300: 87.5%
- UACR 30–<300: 12.1%

0.4% of patients had a UACR <30 mg/g
Albuminuria (UACR) change over time

LS mean ratio to baseline

LS mean ratio: 0.69 (0.66–0.71)*

Placebo
Finerenone

31% reduction in UACR at month 4 with finerenone vs placebo

Data in parenthesis are mean change from baseline, error bars 95% CIs
*Between baseline and month 4 (prespecified secondary outcome); LS, least-squares
Blood pressure and blood glucose

Change in SBP (mmHg) over time

Max delta -3.2 at month 4 vs +0.7 with placebo

Change in HbA1c (%) over time

Mean SBP

Placebo
Finerenone

Mean HbA1c

Months since randomization
Primary endpoint
Kidney failure*, sustained ≥40% decrease in eGFR from baseline, or renal death

HR=0.82 (95% CI 0.73–0.93)
*p=0.0014

*ESKD or an eGFR <15 mL/min/1.73 m²
## Components of the primary kidney-specific composite endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Finerenone (n=2833)</th>
<th>Placebo (n=2841)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite kidney endpoint</strong></td>
<td>504 (17.8)</td>
<td>600 (21.1)</td>
<td>0.82 (0.73–0.93)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>208 (7.3)</td>
<td>235 (8.3)</td>
<td>0.87 (0.72–1.05)</td>
<td>–</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>119 (4.2)</td>
<td>139 (4.9)</td>
<td>0.86 (0.67–1.10)</td>
<td>–</td>
</tr>
<tr>
<td>Sustained eGFR &lt;15 mL/min/1.73 m²</td>
<td>167 (5.9)</td>
<td>199 (7.0)</td>
<td>0.82 (0.67–1.01)</td>
<td>–</td>
</tr>
<tr>
<td>Sustained ≥40% decrease in eGFR from baseline</td>
<td>479 (16.9)</td>
<td>577 (20.3)</td>
<td>0.81 (0.72–0.92)</td>
<td>–</td>
</tr>
<tr>
<td>Renal death</td>
<td>2 (&lt;0.1)</td>
<td>2 (&lt;0.1)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

n refers to number of patients with event
PY, patient-years
Key secondary endpoint
CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF

HR=0.86 (95% CI 0.75–0.99)
*p=0.0339

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo 2841</th>
<th>2653</th>
<th>1969</th>
<th>951</th>
<th>115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finerenone</td>
<td>2833</td>
<td>2688</td>
<td>2017</td>
<td>984</td>
<td>111</td>
</tr>
</tbody>
</table>

Cumulative incidence (%)
# Hierarchical endpoint analysis

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<td>1 Primary kidney composite endpoint</td>
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<td>0.82 (0.73 – 0.93)</td>
<td>0.0014</td>
</tr>
<tr>
<td>2 Key secondary CV composite endpoint</td>
<td>367 (13.0)</td>
<td>420 (14.8)</td>
<td>0.86 (0.75 – 0.99)</td>
<td>0.0339</td>
</tr>
<tr>
<td>3 Death from any cause</td>
<td>219 (7.7)</td>
<td>244 (8.6)</td>
<td>0.90 (0.75 – 1.07)</td>
<td>0.2348</td>
</tr>
<tr>
<td>4 Hospitalization from any cause</td>
<td>1263 (44.6)</td>
<td>1321 (46.5)</td>
<td>0.95 (0.88 – 1.02)</td>
<td>–</td>
</tr>
<tr>
<td>5 Change in UACR*</td>
<td>–</td>
<td>–</td>
<td>0.69 (0.66 – 0.71)*</td>
<td>–</td>
</tr>
<tr>
<td>6 Secondary composite kidney endpoint#</td>
<td>252 (8.9)</td>
<td>326 (11.5)</td>
<td>0.76 (0.65 – 0.90)</td>
<td>–</td>
</tr>
</tbody>
</table>

*n refers to number of patients with event

*Ratio of least-squares mean; #Kidney failure, sustained ≥57% decrease in eGFR from baseline, or renal death (with a ≥57% decrease in eGFR from baseline being equivalent to doubling of serum creatinine)
Efficacy summary

NNT for primary and key secondary endpoints over 3 years

- Modest effects on blood pressure
- Consistent effects on components of primary endpoint
- Consistent effects across key subgroups, including eGFR and UACR at baseline
Investigator-reported treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Safety outcome, n (%)</th>
<th>Finerenone (n=2827)</th>
<th>Placebo (n=2831)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>2468 (87.3)</td>
<td>2478 (87.5)</td>
</tr>
<tr>
<td>AE related to study drug</td>
<td>646 (22.9)</td>
<td>449 (15.9)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>207 (7.3)</td>
<td>168 (5.9)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>902 (31.9)</td>
<td>971 (34.3)</td>
</tr>
<tr>
<td>Serious AE related to study drug</td>
<td>48 (1.7)</td>
<td>34 (1.2)</td>
</tr>
<tr>
<td>Serious AE leading to treatment discontinuation</td>
<td>75 (2.7)</td>
<td>78 (2.8)</td>
</tr>
</tbody>
</table>

Most common AEs leading to treatment discontinuation

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<th>Finerenone (n=2827)</th>
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</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>51 (1.8)</td>
<td>19 (0.7)</td>
</tr>
<tr>
<td>Blood potassium increased</td>
<td>13 (0.5)</td>
<td>6 (0.2)</td>
</tr>
</tbody>
</table>
Change in serum potassium over time

Mean serum $[K^+]$ at baseline:
- Finerenone: $4.4 \pm 0.5$
- Placebo: $4.4 \pm 0.5$

Maximum mean difference in serum potassium between groups = $0.23$ mmol/L at month 4

Data in parenthesis are mean change from baseline; error bars show standard deviation
Investigator-reported treatment-emergent adverse events related to hyperkalemia

- *Using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased'
Investigator-reported treatment-emergent adverse events related to acute kidney injury

Investigator-reported AEs relating to acute kidney injury

Any treatment-emergent AE (%)

- Placebo (n=2831)
  - Any: 129 (4.6%)
  - Related to study drug: 34 (1.2%)
  - Leading to permanent discontinuation: 5 (0.2%)
  - Leading to hospitalization: 53 (1.9%)
  - Leading to death: 0 (0%)

- Finerenone (n=2827)
  - Any: 136 (4.8%)
  - Related to study drug: 18 (0.6%)
  - Leading to permanent discontinuation: 7 (0.2%)
  - Leading to hospitalization: 47 (1.7%)
  - Leading to death: 1 (<0.1%)
Safety summary

In a patient population with advanced CKD on maximally tolerated dose of ACEi/ARB, and excepting temporary withdrawal of study drug, K⁺ management was at the investigator’s discretion:

• Finerenone was well tolerated
• Overall treatment-emergent adverse events were similar between groups
• Finerenone led to a mean increase in serum [K⁺] of 0.2 mmol/L across subpopulations vs placebo

Although hyperkalemia increased, it was manageable; only 2.3% of patients discontinued finerenone vs 0.9% on placebo
Benefit–risk in studies investigating RAS inhibition in similar patient populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy</th>
<th>Median (years)</th>
<th>Permanently discontinued due to hyperkalemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALTITUDE(^1)</strong> (CKD + T2D)</td>
<td>Lack of efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren + ACEi/ARB (n=4272)</td>
<td></td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td>Placebo + ACEi/ARB (n=4285)</td>
<td></td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td>Median 2.7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VA NEPHRON-D(^2)</strong> (CKD + T2D)</td>
<td>Lack of efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi + ARB (n=724)</td>
<td></td>
<td>9.9%</td>
<td></td>
</tr>
<tr>
<td>Placebo + ARB (n=724)</td>
<td></td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>Median 2.2 years</td>
<td></td>
<td></td>
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<tr>
<td><strong>FIDELIO-DKD</strong></td>
<td>Kidney and CV efficacy</td>
<td></td>
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<tr>
<td>Finerenone + ACEi/ARB (n=2827)</td>
<td></td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Placebo + ACEi/ARB (n=2831)</td>
<td></td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Median 2.6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hyperkalemia in VA NEPHRON-D was reported as defined as potassium level >6.0 mEq/L, emergency room visit or admission for hyperkalemia.

Benefit–risk in studies investigating RAAS inhibition in similar patient populations

AMBER\(^1\) (CKD)

<table>
<thead>
<tr>
<th></th>
<th>Placebo + spiro + ACEi/ARB (n=148)</th>
<th>Patiromer + spiro + ACEi/ARB (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy not studied (Phase II)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Permanent discontinuation due to hyperkalemia (%)</strong></td>
<td>23.0%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

**12 weeks**

Kidney and CV efficacy

<table>
<thead>
<tr>
<th></th>
<th>Finerenone + ACEi/ARB (n=2827)</th>
</tr>
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<tbody>
<tr>
<td><strong>Permanent discontinuation due to hyperkalemia (%)</strong></td>
<td>2.3%</td>
</tr>
</tbody>
</table>

**Median 2.6 years**

Overall summary and conclusions

In patients with CKD and T2D treated with optimized RAS therapy, finerenone was well-tolerated and significantly reduced:

- The risk of CKD progression by 18%
- The risk of CV morbidity and mortality by 14%
Thank you

48 countries, 1024 sites, 13,911* participants

Executive committee
George L. Bakris; Gerasimos Filippatos; Rajiv Agarwal; Stefan D. Anker; Luis M. Ruilope; Bertram Pitt

Independent data monitoring committee
Murray Epstein; Aldo Maggioni; Glenn Chertow; Gerald DiBona; Tim Friede; Jose Lopez-Sendon; Jean Rouleau

Clinical event committee
Rajiv Agarwal; Stefan Anker; Phyllis August; Andrew Coats; Hans Diener; Wolfram Döhner; Barry Greenberg; Stephan von Haehling; James Januzzi; Alan Jardine; Carlos Kase; Sankar Navaneethan; Lauren Phillips; Piotr Ponikowski; Pantelis Sarafidis; Titte Srinivas; Turgut Tatlisumak; John Teerlink

National lead investigators
Augusto Vallejos; Richard MacIsaac; Guntram Schernthaner; Pieter Gillard; Maria Eugenia F. Canziani; Theodora Temelkova-Kurktschiev; Ellen Burgess; Sheldon Tobe; Fernando Gonzalez; Zhi-Hong Liu; Andres Angelo’ Cadena Bonfanti; Carlos Francisco Jaramillo; Martin Prazny; Peter Rossing; Jorma Strand; Michel Marre; Roland Schmieder; Christoph Wanner; Pantelis Sarafidis; Juliana Chan; László Rosivall; Joseph Eustace; Ehud Grossman; Yoram Yagiil; Giuseppe Remuzzi; Daisuke Koya; Takashi Wada; Magdalena Madero Rovalo; Ron Gansevoort; Adriaan Kooy; Trine Finnes; Froilan De Leon; Janusz Gumprecht; Fernando Teixeira e Costa; Alexander Drelav; Anantharaman Vathsala; Aslam Amod; Sin Gon Kim; Byung Wan Lee; Julio Pascual Santos; Bengt-Olov Tengmark; Michel Burnier; Chien-Te Lee; Sukit Yamwong; Ramazan Sari; Kieran McCafferty; Borys Mankovsky; Sharon Adler; Linda Fried; Robert Toto; Mark Williams; Tran Quang Khan

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*Number of patients who provided informed consent