Outcomes With Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance: A FIDELITY Subgroup Analysis

POSTER 29-P

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Thomas Ebert,[1] Stefan D. Anker,[2] Luis M. Ruilope,[3-5] Paola Fioretto,[6] Vivian Fonseca,[7] Guillermo E. Umpierrez,[8] Andreas L. Birkenfeld,[9,10] Robert Lawatscheck,[11] Charlie Scott,[12] Katja Rohwedder,[13] and Peter Rossing,[14,15] on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators

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INTRODUCTION

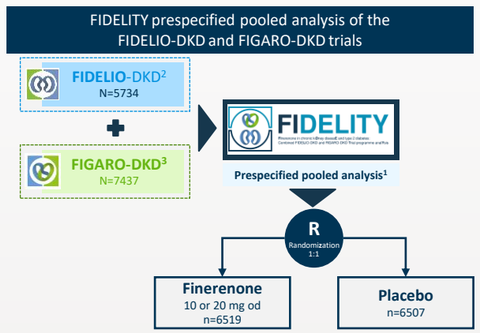
- Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, improved cardiorenal outcomes in a broad population of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELITY prespecified pooled analysis[1] of the FIDELIO-DKD[2] and FIGARO-DKD[3] clinical trials
- This post hoc analysis aimed to explore whether insulin resistance, measured by estimated glucose disposal rate (eGDR), is associated with an increased risk of cardiorenal outcomes and if insulin resistance modifies the cardiorenal efficacy of finerenone

METHODS

- This analysis combines individual patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase 3 clinical trials[2,3]
- FIDELITY study design and efficacy outcomes are shown in **Figure 1** and study population information in **Figure 2**
- Insulin resistance was estimated using the eGDR
- Composite outcomes were analyzed by defined categorical subgroups: eGDR <median and eGDR ≥median
- Safety was also assessed

Figure 1 Study design and efficacy outcomes

STUDY DESIGN



EFFICACY OUTCOMES

Cardiovascular (CV) composite outcome
Time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure

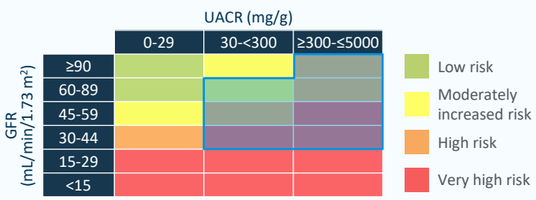
Kidney composite outcome
Time to first onset of kidney failure, sustained ≥57% eGFR decline from baseline over ≥4 weeks, or renal death

eGFR, estimated glomerular filtration rate; IQR, interquartile range; od, once daily.

- Patients included in this FIDELITY post hoc analysis were stratified according to baseline insulin resistance, estimated by eGDR

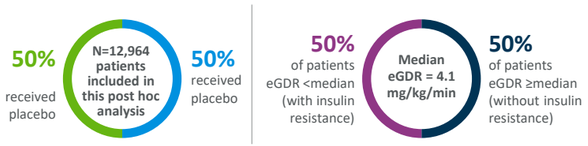
Figure 2 Study population

Key inclusion criteria
- Aged **≥18 years** with **T2D**
- UACR **≥30 to <300** mg/g and eGFR **≥25 to ≤90** mL/min/1.73 m^2, or UACR **≥300 to ≤5000** mg/g and eGFR **≥25** mL/min/1.73 m^2
- Optimized **RAS** blockade for ≥4 weeks
- Serum [K+] **≤4.8** mmol/L



eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; K+, potassium; RAS, renin-angiotensin system; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

RESULTS



- Overall, baseline characteristics were well balanced between groups (**Figure 3**). However, there were some notable differences:
  - Patients with insulin resistance had a longer mean duration of diabetes and a higher urine albumin-to-creatinine ratio (UACR) and mean weight versus those with eGDR ≥median

Figure 3 Patient baseline characteristics according to insulin resistance at baseline

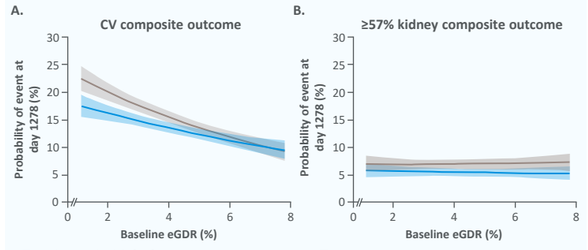
Baseline characteristic	eGDR <median		eGDR ≥median	
	Finerenone (n=3274)	Placebo (n=3237)	Finerenone (n=3238)	Placebo (n=3242)
Age, years, mean	**64.5**	64.6	**64.9**	65
Duration of diabetes, years, mean ± SD	**16.2 ± 8.6**	16.1 ± 8.5	**14.7 ± 8.8**	15.0 ± 8.8
Weight, kg, mean ± SD	**99.1 ± 18.7**	99.3 ± 18.7	**76.9 ± 14.8**	77.0 ± 14.1
eGFR, mL/min/1.73 m², mean ± SD	**57.7 ± 21.9**	57.5 ± 21.9	**57.4 ± 21.3**	57.8 ± 21.6
UACR, mg/g, median	**529.7**	542.8	**494**	492

eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

EFFICACY OUTCOMES (OVERALL GROUP) (FIGURE 4)

- There was a significantly lower risk of CV events at 3.5 years with increasing eGDR (as continuous variable) in the overall group (placebo plus finerenone) (HR 0.88 [95% CI, 0.86-0.91; *P*<0.01])
- However, for kidney outcome events, baseline eGDR had no effect

Figure 4 CV and kidney composite outcomes by continuous variable eGDR



CI, confidence interval; CV, cardiovascular; eGDR, estimated glucose disposal rate.

EFFICACY OUTCOMES BY eGDR SUBGROUPS (FIGURE 5)

- CV and kidney composite outcome incidence rates (IR) were measured per 100 patient-years
  - Similar to the overall group, the IR for CV events was greater if baseline eGDR <median versus IR if baseline eGDR ≥median following either finerenone or placebo treatment
  - The IR of the composite kidney outcome was similar (and therefore followed the trend for the overall population) across eGDR subgroups for both finerenone- or placebo-treated patients
  - The difference in IR between finerenone versus placebo showed no significant heterogeneity by baseline eGFR on the CV outcomes or kidney outcomes (*P*>0.05 for the interaction)

Figure 5 CV and kidney outcomes by baseline eGDR

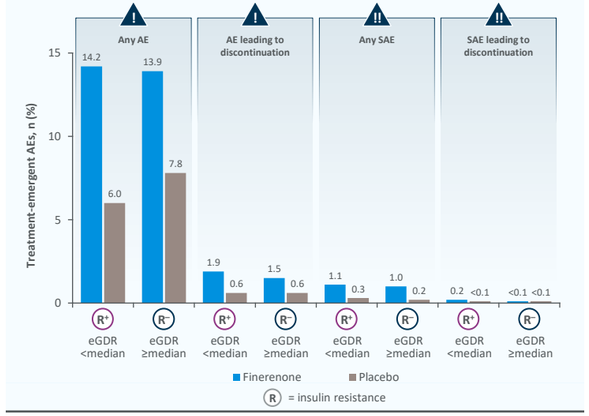
Baseline characteristic	eGDR at baseline: Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	HR (95% CI)	*P* value for interaction
CV composite outcome				
Overall	825/6519 (4.34)	939/6507 (5.01)	0.86 (0.78-0.95)	
eGDR <median	486/3247 (5.18)	577/3237 (6.34)	0.82 (0.72-0.92)	0.29
eGDR ≥median	332/3238 (3.47)	359/3242 (3.76)	0.91 (0.78-1.06)	
Kidney composite outcome				
Overall	360/6519 (1.96)	465/6507 (2.55)	0.77 (0.67-0.88)	
eGDR <median	179/3247 (1.96)	208/3237 (2.31)	0.85 (0.70-1.04)	0.18
eGDR ≥median	180/3238 (1.97)	257/3242 (2.82)	0.69 (0.57-0.84)	

CI, confidence interval; CV, cardiovascular; eGDR, estimated glucose disposal rate; HR, hazard ratio; PY, patient-years.

SAFETY OUTCOMES

- Overall, the incidences of treatment-emergent adverse events and severe adverse events were balanced between the finerenone and placebo groups and between eGDR subgroups
- The incidence of investigator-reported, treatment-emergent hyperkalemia events was higher in patients treated with finerenone versus placebo in both eGDR subgroups, but discontinuations due to hyperkalemia were low (**Figure 6**)

Figure 6 Hyperkalemia safety according to insulin resistance at baseline



AE, adverse event; eGDR, estimated glucose disposal rate; SAE, severe adverse event.

CONCLUSIONS

- **In this post hoc analysis of the FIDELITY prespecified pooled analysis, the efficacy and safety of finerenone were not modified by baseline insulin resistance**
- **A higher risk of CV outcomes, but not kidney outcomes, was observed in people with T2D and CKD who had greater baseline insulin resistance**
- **The safety profile of finerenone was generally consistent irrespective of baseline insulin resistance**

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1. Agarwal R, et al. *Eur Heart J*. 2022;43(6):474-484.
2. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229.
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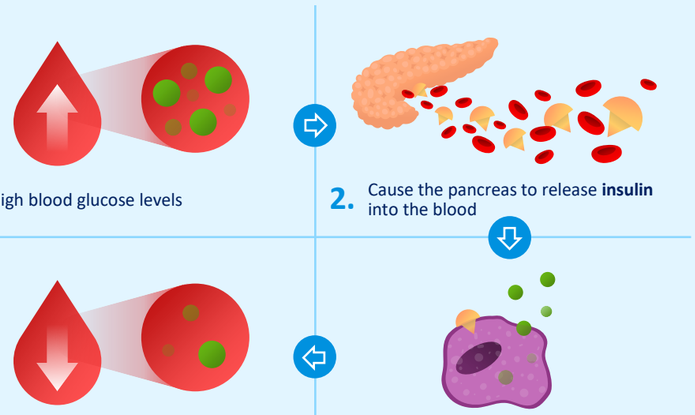
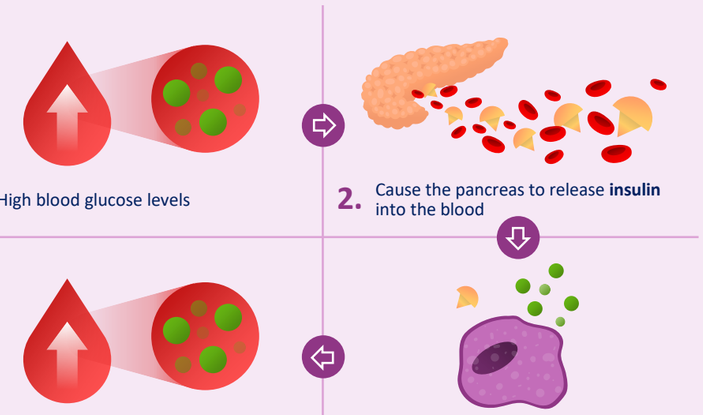
INSULIN RESISTANCE

Example of normal response to high blood glucose levels



Example of <u>normal response</u> to high blood glucose levels such as may happen after eating a large, starchy meal

Example of insulin resistance leading to ongoing high glucose levels



Insulin resistance is associated with increased risk of T2D, cardiovascular disease, and CKD[1-4]

CKD, chronic kidney disease; T2D, type 2 diabetes

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1. Whaley-Connell A, Sowers JR. *Cardiorenal Med*. 2017;8(1):41-49.
2. Schrauben SJ, et al. *BMC Nephrol*. 2019;20(1):60.
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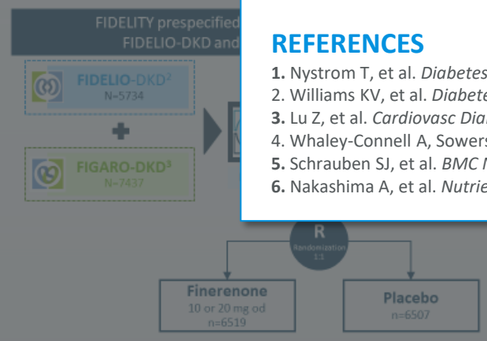

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Baseline characteristic | **eGDR at baseline**

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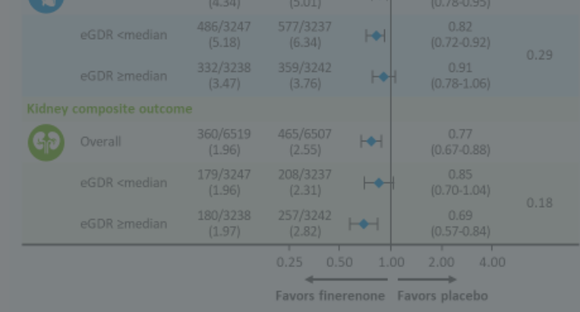

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0.25 0.50 1.00 2.00 4.00
Favors finerenone Favors placebo

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THE ESTIMATED GLUCOSE DISPOSAL RATE (eGDR)

- The eGDR is an inverse marker of insulin action (in vivo) and was originally developed as a validated score to measure insulin resistance in patients with type 1 diabetes based on waist circumference, hypertension, and glycated hemoglobin level (HbA1c)[1-3]
- In this post hoc analysis, insulin resistance was estimated using the eGDR and was calculated as follows: 21.158 + (−0.09 x waist circumference [cm]) + (−3.407 x presence of hypertension) + (−0.551 x HbA1c [%])
  - A lower eGDR is associated with greater insulin resistance and increased risk of CV disease and progression to end-stage kidney disease versus a higher eGDR[4-6]

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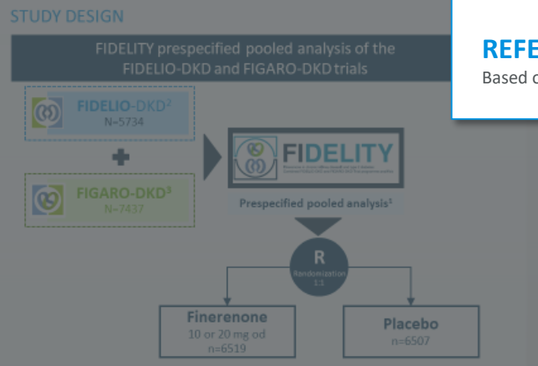

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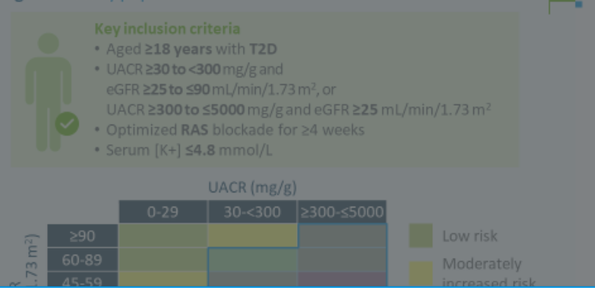
Figure 2 Study population



- Patients with insulin resistance had a longer mean duration of diabetes and a higher urine albumin-to-creatinine ratio (UACR) and mean weight versus those with eGDR ≥median

Figure 3 Patient baseline characteristics according to insulin resistance at baseline

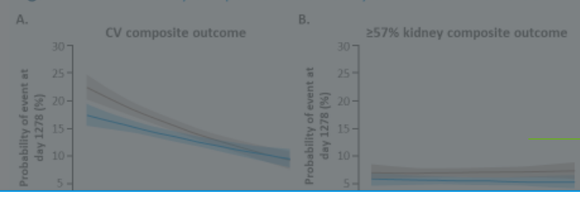
Baseline characteristic	eGDR at baseline			
	eGDR <median		eGDR ≥median	
	Finerenone (n=3274)	Placebo (n=3237)	Finerenone (n=3238)	Placebo (n=3242)
Age, years, mean	64.5	64.6	64.9	65
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
Weight, kg, mean ± SD	99.1 ± 18.7	99.3 ± 18.7	76.9 ± 14.8	77.0 ± 14.1
eGFR, mL/min/1.73 m², mean ± SD	57.7 ± 21.9	57.5 ± 21.9	57.4 ± 21.3	57.8 ± 21.6
UACR, mg/g, median	529.7	542.8	494	492

eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

EFFICACY OUTCOMES (OVERALL GROUP) (FIGURE 4)

- There was a significantly lower risk of CV events at 3.5 years with increasing eGDR (as continuous variable) in the overall group (placebo plus finerenone) (HR 0.88 [95% CI, 0.86-0.91; *P*<0.01])
- However, for kidney outcome events, baseline eGDR had no effect

Figure 4 CV and kidney composite outcomes by continuous variable eGDR



- The difference in IR between finerenone versus placebo showed no significant heterogeneity by baseline eGFR on the CV outcomes or kidney outcomes (*P*>0.05 for the interaction)

Figure 5 CV and kidney outcomes by baseline eGDR

Baseline characteristic	eGDR at baseline: Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	HR (95% CI)	*P* value for interaction
CV composite outcome				
Overall	825/6519 (4.34)	939/6507 (5.01)	0.86 (0.78-0.95)	
eGDR <median	486/3247 (5.18)	577/3237 (6.34)	0.82 (0.72-0.92)	0.29
eGDR ≥median	332/3238 (3.47)	359/3242 (3.76)	0.91 (0.78-1.06)	
Kidney composite outcome				
Overall	360/6519 (1.96)	465/6507 (2.55)	0.77 (0.67-0.88)	
eGDR <median	179/3247 (1.96)	208/3237 (2.31)	0.85 (0.70-1.04)	0.18
eGDR ≥median	180/3238 (1.97)	257/3242 (2.82)	0.69 (0.57-0.84)	

0.25 0.50 1.00 2.00 4.00
Favors finerenone Favors placebo

CI, confidence interval; CV, cardiovascular; eGDR, estimated glucose disposal rate; HR, hazard ratio; PY, patient-years.

SAFETY OUTCOMES

- Overall, the incidences of treatment-emergent adverse events and severe adverse events were balanced between the finerenone and placebo groups and between eGDR subgroups
- The incidence of investigator-reported, treatment-emergent hyperkalemia events was higher in patients treated with finerenone versus placebo in both eGDR subgroups, but discontinuations due to hyperkalemia were low (**Figure 6**)

Figure 6 Hyperkalemia safety according to insulin resistance at baseline

estimated glucose disposal rate; SAE, severe adverse event.

EFFICACY OUTCOMES CONTINUED

- **Kidney failure** was defined as end-stage kidney disease (initiation of long-term dialysis for ≥90 days, kidney transplantation, or a sustained decrease in estimated glomerular filtration rate [eGFR] to <15 mL/min/1.73 m²)

CONCLUSIONS

- In this post hoc analysis of the FIDELITY prespecified pooled analysis, the efficacy and safety of finerenone were not modified by baseline insulin resistance
- A higher risk of CV outcomes, but not kidney outcomes, was observed in people with T2D and CKD who had greater baseline insulin resistance
- The safety profile of finerenone was generally consistent irrespective of baseline insulin resistance

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REFERENCES

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Outcomes With Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance: A FIDELITY Subgroup Analysis

POSTER 29-P

THIS POSTER IS INTERACTIVE

Click for supplementary content where you see this icon:

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INTRODUCTION

- Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, improved cardiorenal outcomes in a broad population of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELITY prespecified pooled analysis[1] of the FIDELIO-DKD[2] and FIGARO-DKD[3] clinical trials
- This post hoc analysis aimed to explore whether insulin resistance, measured by estimated glucose disposal rate (eGDR), is associated with an increased risk of cardiorenal outcomes and if insulin resistance modifies the cardiorenal efficacy of finerenone

METHODS

- This analysis combines individual patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase 3 clinical trials[2,3]
- FIDELITY study design and efficacy outcomes are shown in and study population information in **Figure 2**
- Insulin resistance was estimated using the eGDR
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- Safety was also assessed

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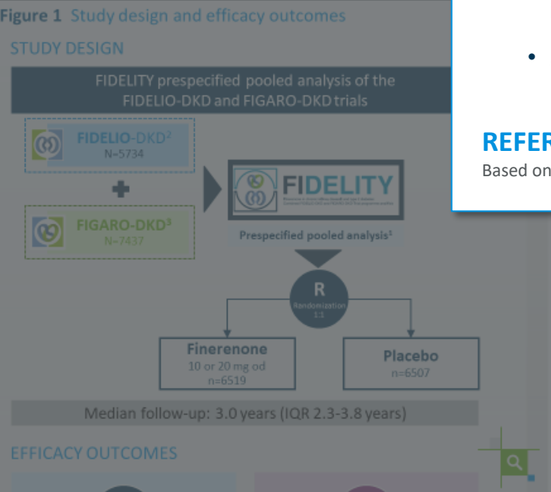

eGFR, estimated glomerular filtration rate; IQR, interquartile range; od, once daily.

- Patients included in this FIDELITY post hoc analysis were stratified according to baseline insulin resistance, estimated by eGDR

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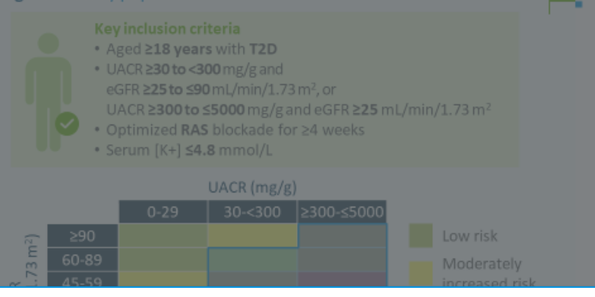

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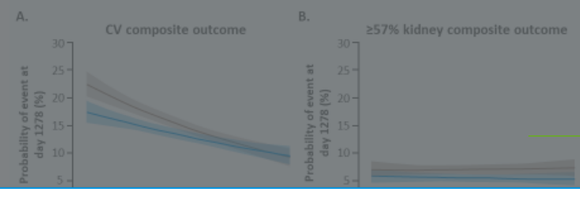

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SAFETY OUTCOMES

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- The incidence of investigator-reported, treatment-emergent hyperkalemia events was higher in patients treated with finerenone versus placebo in both eGDR subgroups, but discontinuations due to hyperkalemia were low (**Figure 6**)

Figure 6 Hyperkalemia safety according to insulin resistance at baseline

estimated glucose disposal rate; SAE, severe adverse event.

ASSESSMENT OF SAFETY

- Safety outcomes and vital signs evaluations included assessment of adverse events and central laboratory testing
- Adverse events that occurred during the treatment period were defined as those that started or worsened during study drug intake or up to 3 days after any temporary or permanent interruption
- All outcomes were adjudicated by independent clinical event committees blinded to treatment assignment

CONCLUSIONS

- In this post hoc analysis of the FIDELITY prespecified pooled analysis, the efficacy and safety of finerenone were not modified by baseline insulin resistance
- A higher risk of CV outcomes, but not kidney outcomes, was observed in people with T2D and CKD who had greater baseline insulin resistance
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- This post hoc analysis aimed to explore whether insulin resistance, measured by estimated glucose disposal rate (eGDR), is associated with an increased risk of cardiorenal outcomes and if insulin resistance modifies the cardiorenal efficacy of finerenone

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- This analysis combines individual patient-level data from t FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545 phase 3 clinical trials[2,3]
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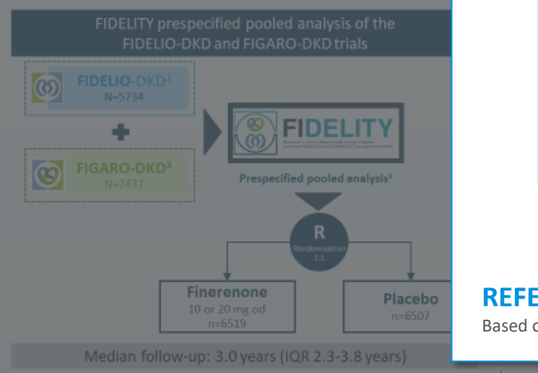
Figure 1 Study design and efficacy outcomes

STUDY DESIGN



EFFICACY OUTCOMES

Cardiovascular (CV) composite outcome
Time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure

Kidney composite outcome
Time to first onset of kidney failure, sustained ≥57% eGFR decline from baseline over ≥4 weeks, or renal death

eGFR, estimated glomerular filtration rate; IQR, interquartile range; od, once daily.

- Patients included in this FIDELITY post hoc analysis were stratified according to baseline insulin resistance, estimated by eGDR

Figure 2 Study population

Key inclusion criteria
- Aged **≥18 years** with **T2D**
- UACR **≥30 to <300** mg/g and eGFR **≥25 to ≤90** mL/min/1.73 m², or UACR **≥300 to ≤5000** mg/g and eGFR **≥25** mL/min/1.73 m²
- Optimized **RAS** blockade for ≥4 weeks

Age, years, mean	64.5	64.6	64.9	65
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
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Figure 4 CV and kidney composite outcomes by continuous variable eGDR

	Finerenone	Placebo	HR (95% CI)	P for interaction
CV composite outcome				
Overall	486/3247 (5.18)	577/3237 (6.34)	0.82 (0.72-0.92)	
eGDR <median	486/3247 (5.18)	577/3237 (6.34)	0.82 (0.72-0.92)	0.29
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Kidney composite outcome				
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afety according to insulin resistance at baseline

estimated glucose disposal rate; SAE, severe adverse event.

ADDITIONAL INCLUSION CRITERIA

- The use of insulin and other oral antidiabetics, including:

Orals:

- Dipeptidyl peptidase-4 inhibitors
- Sodium glucose cotransporter-2 inhibitors
- Biguanides
- Alpha-glucosidase inhibitors
- Meglitinides
- Thiazolidinediones
- Sulfonylureas

Injection:

- Insulin
- Glucagon-like peptide-1 receptor agonists

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LUSIONS

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KEY EXCLUSION CRITERIA

Key inclusion criteria

- **HFrEF** with **NYHA Class II-IV**
- Uncontrolled **arterial hypertension**
- HbA1c **>12%**
- **Other** kidney disease

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STUDY DESIGN

FIDELITY prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials

FIDELIO-DKD[2] N=5734 + FIGARO-DKD[3] N=7437 → FIDELITY Prespecified pooled analysis[1]

Finerenone 10 or 20 mg od n=6519; Placebo n=6507

Median follow-up: 3.0 years (IQR 2.3-3.8 years)

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Cardiovascular (CV) composite outcome Time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure

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Outcomes With Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance: A FIDELITY Subgroup Analysis

POSTER 29-P

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PATIENT BASELINE CHARACTERISTICS ACCORDING TO INSULIN RESISTANCE AT BASELINE

Baseline characteristic	eGDR at baseline			
	eGDR <median		eGDR ≥median	
	Finerenone (n=3247)	Placebo (n=3237)	Finerenone (n=3238)	Placebo (n=3242)
Age, years, mean	64.5	64.6	64.9	65
Sex, female, n (%)	926 (28.5)	897 (27.7)	1096 (33.8)	992 (30.6)
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
HbA1c, %, mean ± SD	8.2 ± 1.4	8.2 ± 1.4	7.2 ± 1.1	7.2 ± 1.1
BMI, kg/m^2, mean ± SD	34.6 ± 5.7	34.6 ± 5.6	28.1 ± 4.4	28.0 ± 4.3
Weight, kg, mean ± SD	99.1 ± 18.7	99.3 ± 18.7	76.9 ± 14.8	77.0 ± 14.1
SBP, mmHg, mean ± SD	138.5 ± 14.0	138.1 ± 13.9	136.1 ± 14.1	135.3 ± 14.5
History of CV disease, n (%)	1565 (48.2)	1615 (49.9)	1396 (43.1)	1331 (41.1)
eGFR, mL/min/1.73 m^2, mean ± SD	57.7 ± 21.9	57.5 ± 21.9	57.4 ± 21.3	57.8 ± 21.6
UACR, mg/g, median	529.7	542.8	494	492
Serum potassium, mmol/L, mean ± SD	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.5

BMI, body mass index; CV, cardiovascular; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

- Additionally, a greater proportion of patients in the eGDR <median subgroup were of White race compared with the eGDR ≥median subgroup (80% vs 56%), while a substantially lower proportion were of Asian race (9% vs 35%)

REFERENCE

Based on overview provided by Ebert T, et al. *Diabetes Care*. 2023.

INTRODUCTION

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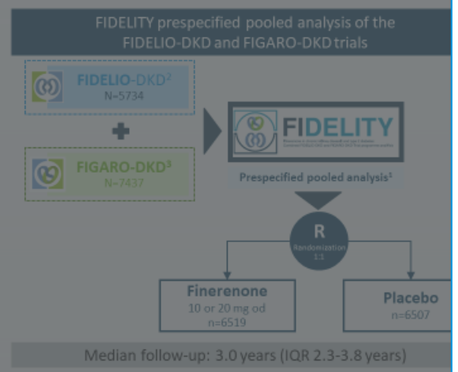

EFFICACY OUTCOMES

Cardiovascular (CV) composite outcome
Time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure

Kidney composite outcome
Time to first onset of kidney failure, sustained ≥57% eGFR decline from baseline over ≥4 weeks, or renal death

eGFR, estimated glomerular filtration rate; IQR, interquartile range; od, once daily.

- Patients included in this FIDELITY post hoc analysis were stratified according to baseline insulin resistance, estimated by eGDR

EFFICACY OUTCOMES (OVERALL GROUP) (FIGURE 4)

- There was a significantly lower risk of CV events at 3.5 years with

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- Ov… of treatment-emergent adverse events …nts were balanced between the finerenone …d between eGDR subgroups
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Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
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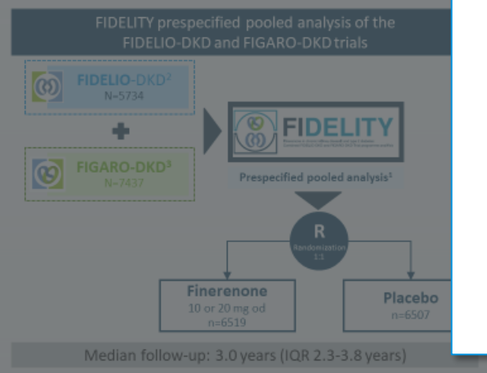

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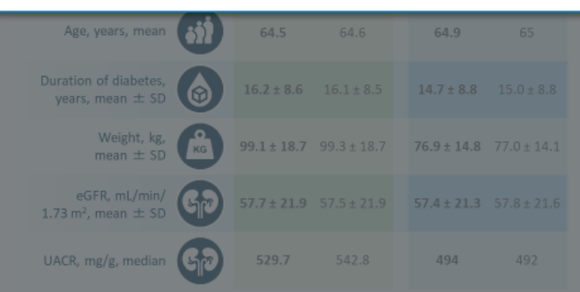
- The safety profile of finerenone was generally consistent irrespective of baseline insulin resistance

PATIENT BASELINE MEDICATIONS AND GLUCOSE-LOWERING THERAPIES

Baseline characteristic	eGDR at baseline			
	eGDR <median		eGDR ≥median	
	Finerenone (n=3247)	Placebo (n=3237)	Finerenone (n=3238)	Placebo (n=3242)
Baseline medications, n (%)				
ACE inhibitors	1483 (45.7)	1516 (46.8)	1290 (39.8)	1315 (40.6)
ARBs	2015 (62.1)	2045 (63.2)	2173 (67.1)	2179 (67.2)
Beta blockers	2226 (68.6)	2241 (69.2)	1584 (48.9)	1665 (51.4)
Diuretics	2446 (75.3)	2495 (77.1)	1809 (55.9)	1873 (57.8)
Statins	2672 (82.3)	2681 (82.8)	2448 (75.6)	2498 (77.1)
Potassium supplements	337 (10.4)	376 (11.6)	230 (7.1)	289 (8.9)
Potassium-lowering agents	245 (7.5)	142 (4.4)	281 (8.7)	197 (6.1)
Glucose-lowering therapies, n (%)				
Insulin and analogs	2298 (70.8)	2229 (68.9)	1551 (47.9)	1519 (46.9)
Sulfonylureas	769 (23.7)	760 (23.5)	914 (28.2)	933 (28.8)
DPP-4 inhibitors	704 (21.7)	698 (21.6)	951 (29.4)	909 (28.0)
GLP-1RAs	356 (11.0)	300 (9.3)	137 (4.2)	144 (4.4)
SGLT-2 inhibitors	275 (8.5)	268 (8.3)	162 (5.0)	170 (5.2)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4; dipeptidyl peptidase-4; eGDR, estimated glucose disposal rate; GLP-1RA; glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; SGLT-2, sodium-glucose co-transporter-2.



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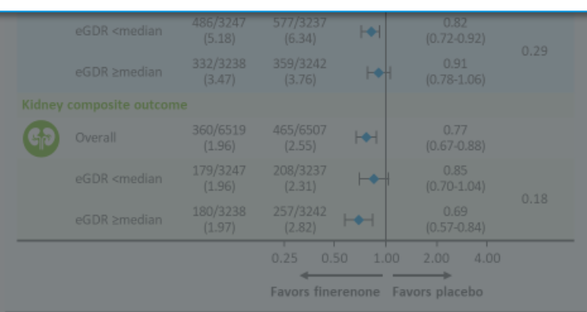

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INTRODUCTION

- Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, improved cardiorenal outcomes in a broad population of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELITY prespecified pooled analysis[1] of the FIDELIO-DKD[2] and FIGARO-DKD[3] clinical trials
- This post hoc analysis aimed to explore whether insulin resistance, measured by estimated glucose disposal rate (eGDR), is associated with an increased risk of cardiorenal outcomes and if insulin resistance modifies the cardiorenal efficacy of finerenone

METHODS

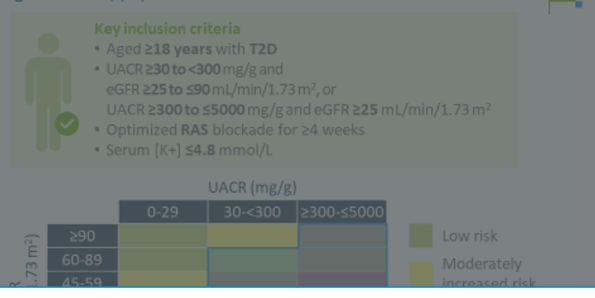
- This analysis combines individual patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase 3 clinical trials[2,3]
- FIDELITY study design and efficacy outcomes are shown in and study population information in **Figure 2**
- Insulin resistance was estimated using the eGDR
- Composite outcomes were analyzed by defined categoric subgroups: eGDR <median and eGDR ≥median
- Safety was also assessed

Figure 1 Study design and efficacy outcomes

eGFR, estimated glomerular filtration rate; IQR, interquartile range; od, once daily.

- Patients included in this FIDELITY post hoc analysis were stratified according to baseline insulin resistance, estimated by eGDR

Figure 2 Study population



- Overall, baseline characteristics were well balanced between groups (**Figure 3**). However, there were some notable differences:
  - Patients with insulin resistance had a longer mean duration of diabetes and a higher urine albumin-to-creatinine ratio (UACR) and mean weight versus those with eGDR ≥median

Figure 3 Patient baseline characteristics according to insulin resistance at baseline

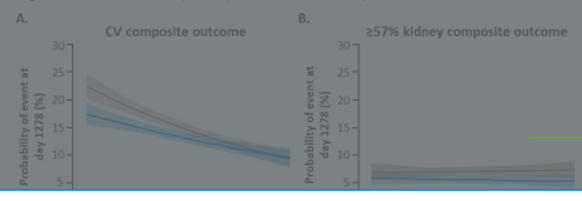
Baseline characteristic	eGDR at baseline			
	eGDR <median		eGDR ≥median	
	Finerenone (n=3274)	Placebo (n=3237)	Finerenone (n=3238)	Placebo (n=3242)
Age, years, mean	64.5	64.6	64.9	65
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
Weight, kg, mean ± SD	99.1 ± 18.7	99.3 ± 18.7	76.9 ± 14.8	77.0 ± 14.1
eGFR, mL/min/1.73 m², mean ± SD	57.7 ± 21.9	57.5 ± 21.9	57.4 ± 21.3	57.8 ± 21.6
UACR, mg/g, median	529.7	542.8	494	492

eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

EFFICACY OUTCOMES (OVERALL GROUP) (FIGURE 4)

- There was a significantly lower risk of CV events at 3.5 years with increasing eGDR (as continuous variable) in the overall group (placebo plus finerenone) (HR 0.88 [95% CI, 0.86-0.91; *P*<0.01])
- However, for kidney outcome events, baseline eGDR had no effect

Figure 4 CV and kidney composite outcomes by continuous variable eGDR



- The IR of the composite kidney outcome was similar (and therefore followed the trend for the overall population) across eGDR subgroups for both finerenone- or placebo-treated patients
- The difference in IR between finerenone versus placebo showed no significant heterogeneity by baseline eGFR on the CV outcomes or kidney outcomes (*P*>0.05 for the interaction)

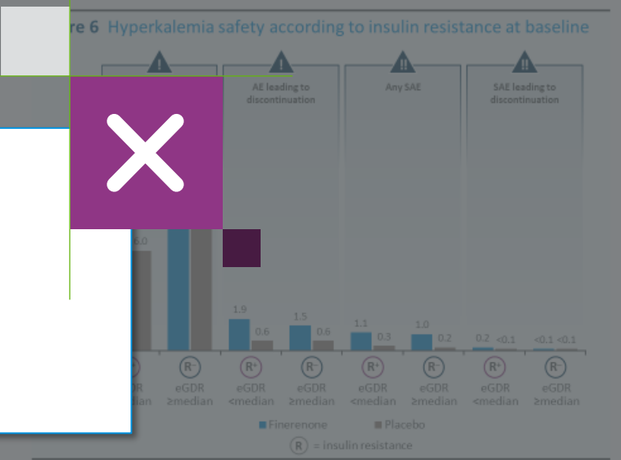
Figure 5 CV and kidney outcomes by baseline eGDR

CI, confidence interval; CV, cardiovascular; eGDR, estimated glucose disposal rate; HR, hazard ratio; PY, patient-years.

SAFETY OUTCOMES

- Overall, the incidences of treatment-emergent adverse events and severe adverse events were balanced between the finerenone and placebo groups and between eGDR subgroups
- The incidence of investigator-reported, treatment-emergent hyperkalemia events was higher in patients treated with finerenone versus placebo in both eGDR subgroups, but discontinuations due to hyperkalemia were low (**Figure 6**)

Figure 6 Hyperkalemia safety according to insulin resistance at baseline



AE, adverse event; eGDR, estimated glucose disposal rate; SAE, severe adverse event.

SENSITIVITY ANALYSES

- Consistent strength and direction of the associations were observed across sensitivity analyses using alternative measures of insulin resistance (baseline triglyceride/high-density lipoprotein ratio, visceral adiposity index, and lipid accumulation product index)

CONCLUSIONS

- In this post hoc analysis of the FIDELITY prespecified pooled analysis, the efficacy and safety of finerenone were not modified by baseline insulin resistance
- A higher risk of CV outcomes, but not kidney outcomes, was observed in people with T2D and CKD who had greater baseline insulin resistance
- The safety profile of finerenone was generally consistent irrespective of baseline insulin resistance

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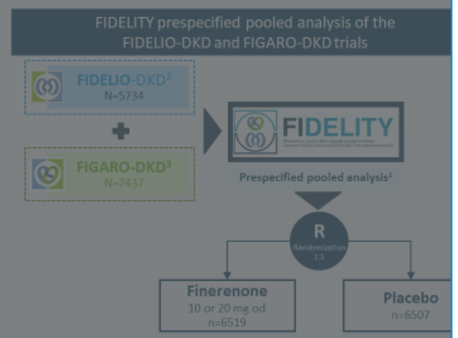

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Time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure

Kidney composite outcome
Time to first onset of kidney failure, sustained ≥57% eGFR decline from baseline over ≥4 weeks, or renal death

eGFR, estimated glomerular filtration rate; IQR, interquartile range; od, once daily.

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EFFICACY OUTCOMES (OVERALL GROUP) (FIGURE 4)

- There was a significantly lower risk of CV events at 3.5 years with …

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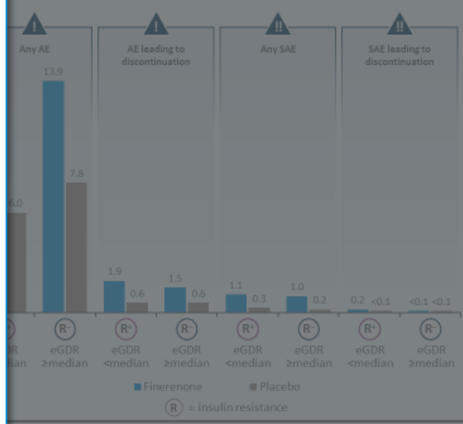

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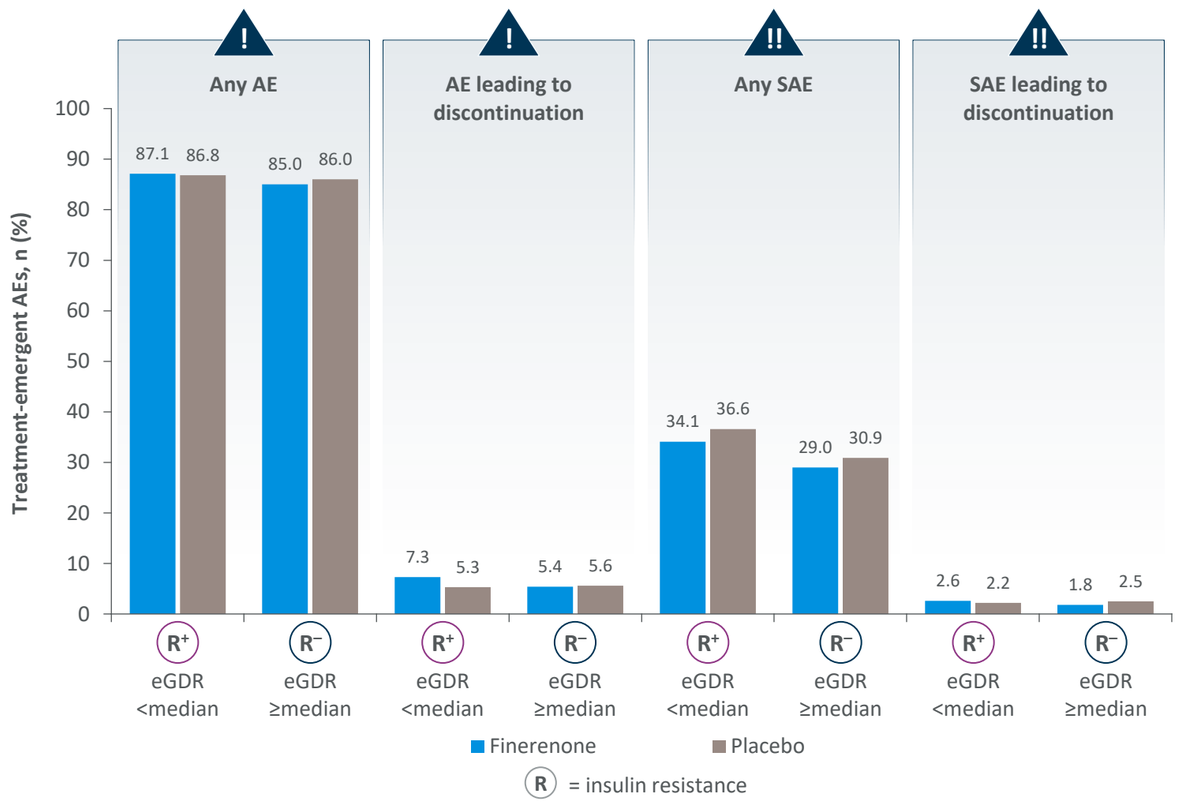
TREATMENT-EMERGENT ADVERSE EVENTS ACCORDING TO INSULIN RESISTANCE AT BASELINE



AE, adverse event; eGDR, estimated glucose disposal rate; SAE, severe adverse event.

years, mean ± SD				
Weight, kg, mean ± SD	99.1 ± 18.7	99.3 ± 18.7	76.9 ± 14.8	77.0 ± 14.1
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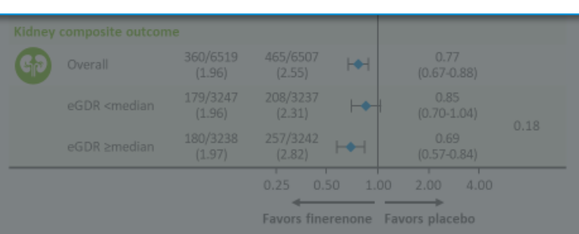

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Outcomes With Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance: A FIDELITY Subgroup Analysis

POSTER 29-P

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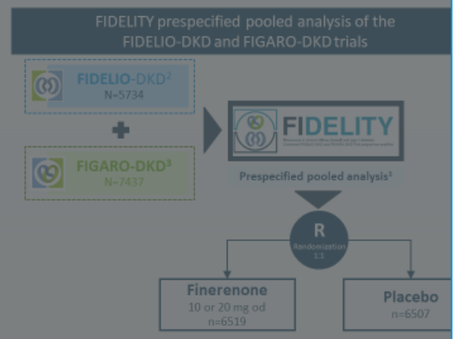
- Safety was also assessed

Figure 1 Study design and efficacy outcomes

STUDY DESIGN



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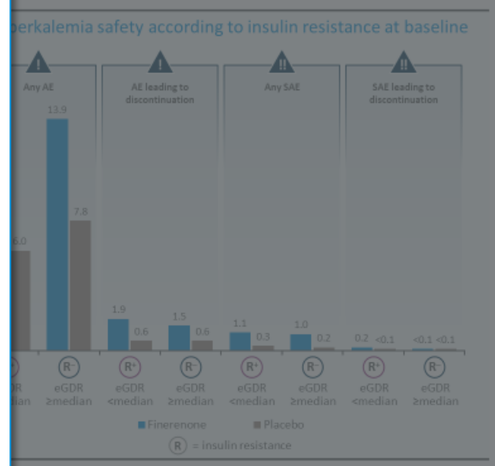

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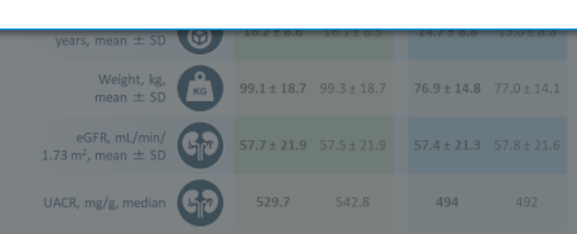
- …afety profile of finerenone was generally consistent irrespective of baseline insulin resistance

Baseline characteristic	eGDR at baseline			
	eGDR <median		eGDR ≥median	
n (%)	Finerenone (n=3242)	Placebo (n=3228)	Finerenone (n=3235)	Placebo (n=3234)
Treatment-emergent AEs				
Any AE	2823 (87.1)	2801 (86.8)	2751 (85.0)	2781 (86.0)
Study drug–related AE	640 (19.7)	457 (14.2)	560 (17.3)	402 (12.4)
AE leading to discontinuation	236 (7.3)	170 (5.3)	176 (5.4)	180 (5.6)
Any SAE	1107 (34.1)	1181 (36.6)	937 (29.0)	999 (30.9)
Study drug–related SAE	46 (1.4)	32 (1.0)	36 (1.1)	29 (0.9)
SAE leading to discontinuation	84 (2.6)	72 (2.2)	59 (1.8)	82 (2.5)
Fatal AE	55 (1.7)	83 (2.6)	54 (1.7)	68 (2.1)
Treatment-emergent hyperkalemia events				
Any AE	460 (14.2)	195 (6.0)	449 (13.9)	252 (7.8)
Study drug–related AE	286 (8.8)	107 (3.3)	285 (8.8)	142 (4.4)
AE leading to discontinuation	63 (1.9)	19 (0.6)	47 (1.5)	19 (0.6)
Any SAE	36 (1.1)	11 (0.3)	32 (1.0)	5 (0.2)
Study drug–related SAE	22 (0.7)	6 (0.2)	20 (0.6)	2 (<0.1)
SAE leading to discontinuation	8 (0.2)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Fatal AE	0	0	0	0

AE, adverse event; eGDR, estimated glucose disposal rate; SAE, severe adverse event.



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- Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, improved cardiorenal outcomes in a broad population of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELITY prespecified pooled analysis[1] of the FIDELIO-DKD[2] and FIGARO-DKD[3] clinical trials
- This post hoc analysis aimed to explore whether insulin resistance, measured by estimated glucose disposal rate (eGDR), is associated with an increased risk of cardiorenal outcomes and if insulin resistance modifies the cardiorenal efficacy of finerenone

METHODS

- This analysis combines individual patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545 phase 3 clinical trials[2,3]
- FIDELITY study design and efficacy outcomes are shown in and study population information in **Figure 2**
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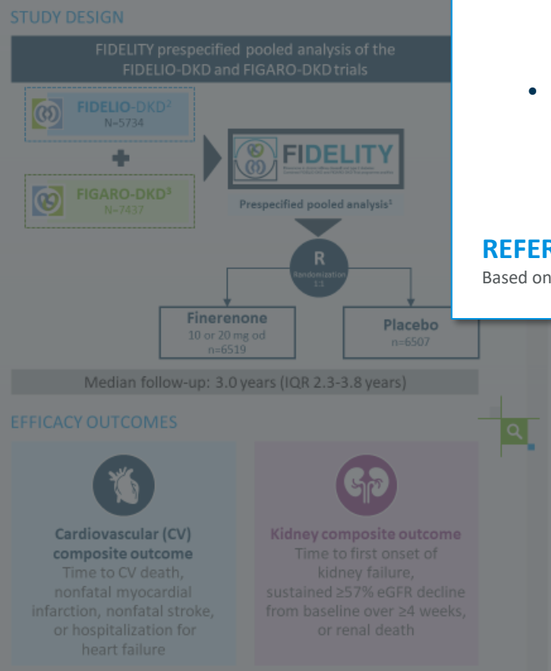

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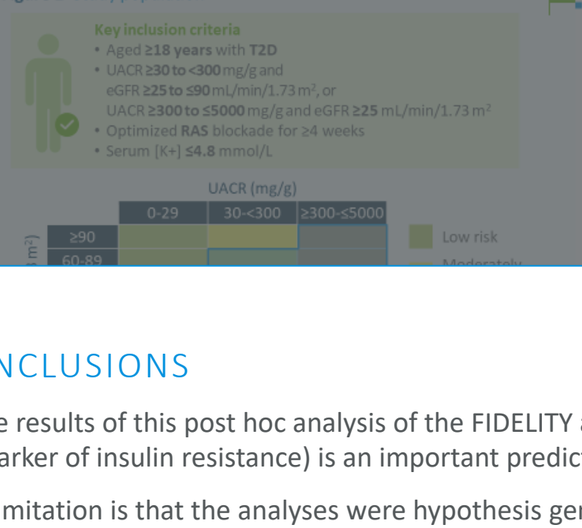


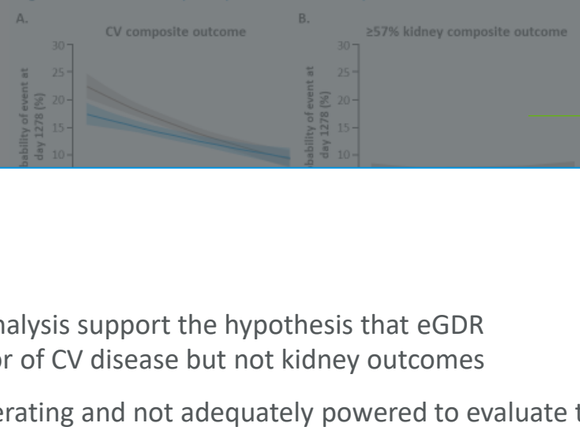
	Finerenone (n=3274)	Placebo (n=3237)	Finerenone (n=3238)	Placebo (n=3242)
Age, years, mean	64.5	64.6	64.9	65
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
Weight, kg, mean ± SD	99.1 ± 18.7	99.3 ± 18.7	76.9 ± 14.8	77.0 ± 14.1
eGFR, mL/min/1.73 m², mean ± SD	57.7 ± 21.9	57.5 ± 21.9	57.4 ± 21.3	57.8 ± 21.6
UACR, mg/g, median	529.7	542.8	494	492

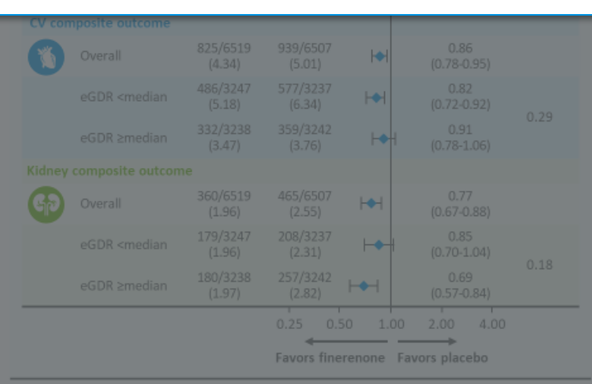
eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

EFFICACY OUTCOMES (OVERALL GROUP) (FIGURE 4)

- There was a significantly lower risk of CV events at 3.5 years with increasing eGDR (as continuous variable) in the overall group (placebo plus finerenone) (HR 0.88 [95% CI, 0.86-0.91; *P*<0.01])
- However, for kidney outcome events, baseline eGDR had no effect

Figure 4 CV and kidney composite outcomes by continuous variable eGDR



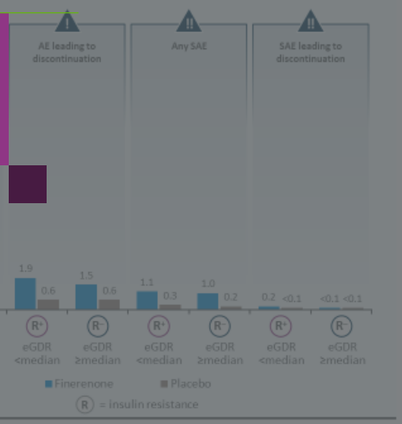


CI, confidence interval; CV, cardiovascular; eGDR, estimated glucose disposal rate; HR, hazard ratio; PY, patient-years.

SAFETY OUTCOMES

- Overall, the incidences of treatment-emergent adverse events and severe adverse events were balanced between the finerenone and placebo groups and between eGDR subgroups
- The incidence of investigator-reported, treatment-emergent hyperkalemia events was higher in patients treated with finerenone versus placebo in both eGDR subgroups, but discontinuations due to hyperkalemia were low (**Figure 6**)

Figure 6 Hyperkalemia safety according to insulin resistance at baseline



estimated glucose disposal rate; SAE, severe adverse event.

CONCLUSIONS

- The results of this post hoc analysis of the FIDELITY analysis support the hypothesis that eGDR (marker of insulin resistance) is an important predictor of CV disease but not kidney outcomes
- A limitation is that the analyses were hypothesis generating and not adequately powered to evaluate the statistical significance of any associations between eGDR with CV and kidney outcomes. This needs to be investigated in further studies, including randomized clinical trials
- In addition, further studies are required to examine whether the hemodynamic effects of insulin resistance in the kidneys differ between individuals with diabetes versus patients with advanced CKD with or without diabetes

REFERENCE

Based on overview provided by Ebert T, et al. *Diabetes Care*. 2023.

LUSIONS

s post hoc analysis of the FIDELITY prespecified d analysis, the efficacy and safety of finerenone not modified by baseline insulin resistance

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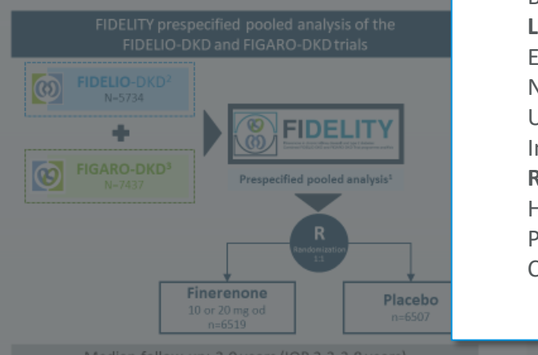

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- Patients included in this FIDELITY post hoc analysis were stratified according to baseline insulin resistance, estimated by eGDR

Figure 2 Study population

Key inclusion criteria
- Aged **≥18 years** with **T2D**
- UACR **≥30 to <300** mg/g and eGFR **≥25 to ≤90** mL/min/1.73 m², or UACR **≥300 to ≤5000** mg/g and eGFR **≥25** mL/min/1.73 m²

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Age, years, mean	64.5	64.6	64.9	65
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	15.0 ± 8.8
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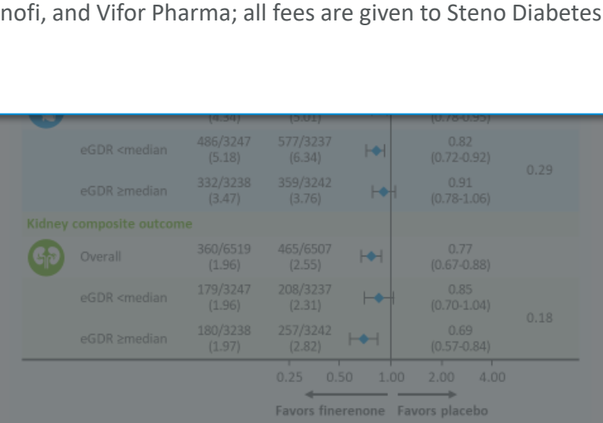

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ACKNOWLEDGMENTS

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