61ST ERA CONGRESS
STOCKHOLM & VIRTUAL
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Hyperkalaemia risk and the effect of finerenone in patients with diabetes and chronic kidney disease: an analysis from FIDELITY

Presented by Peter Rossing, MD

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On behalf of João P. Ferreira, Stefan D. Anker, Biff F. Palmer, Bertram Pitt, Luis M. Ruilope, Christoph Wanner, Youssef M.K. Farag, Andrea Horvat-Broecker, Marc Lambelet, Meike Brinker, Katja Rohwedder, Gerasimos Filippatos, and the FIDELIO-DKD and FIGARO-DKD Investigators

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Disclosures

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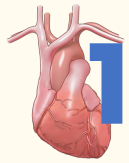
- All fees are given to Steno Diabetes Center Copenhagen

Finerenone is a selective, nonsteroidal MRA that has demonstrated CV and kidney benefit in patients with CKD and T2D[1–3]

FIDELIO-DKD[2] (N=5662*) + **FIGARO**-DKD[3] (N=7328*) = **FIDELITY**[1] (N=12,990*)

Eligibility criteria:

- ✓ T2D
- ✓ CKD
- ✓ On maximum tolerated dose of a single RASi
- ✓ Serum [K^+] ≤4.8 mmol/l
- ✗ Chronic Symptomatic HFrEF

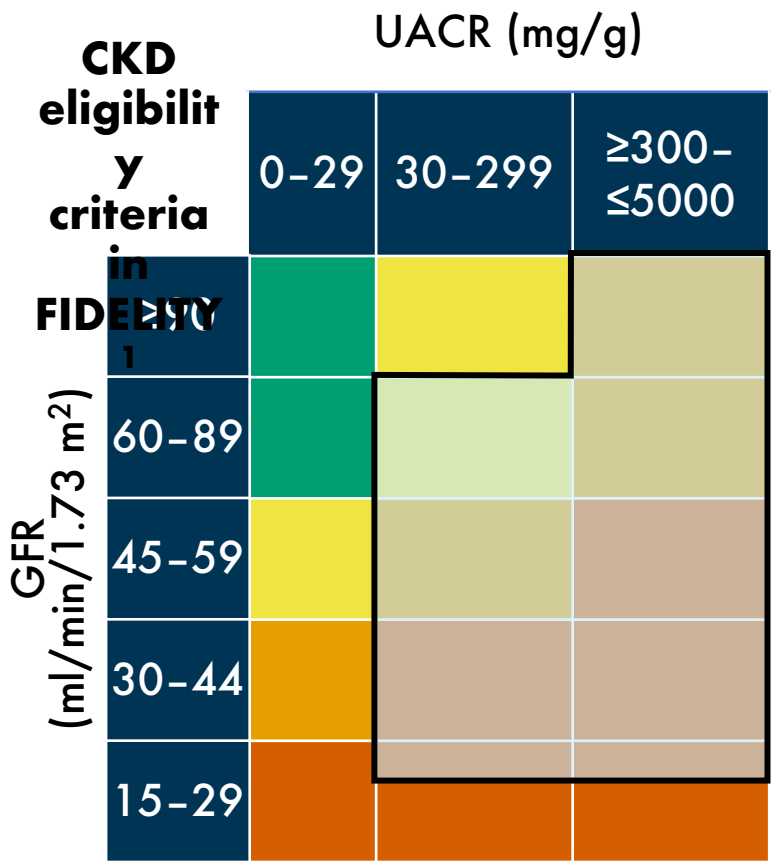


14%

Risk of the CV composite outcome of time to CV death, non-fatal MI, non-fatal stroke or HHF versus placebo
HR=0.86; 95% CI 0.78–0.95; *p*=0.0018

24%

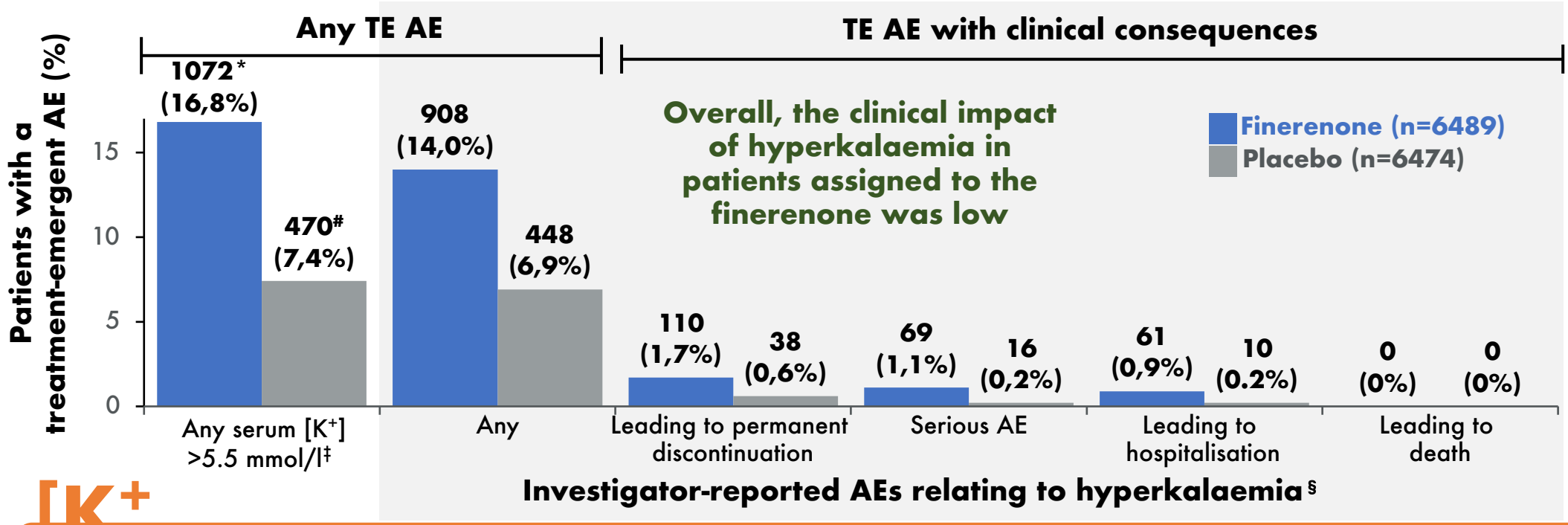
Risk of the kidney composite outcome of time to kidney failure, sustained ≥57% decrease in eGFR from baseline or kidney death versus placebo
HR=0.76; 95% CI 0.66–0.88; *p*=0.0001



*Patients analysed without critical Good Clinical Practice violations. CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; HR, hazard ratio; [K^+], potassium concentration; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 3. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

In FIDELITY, finerenone was associated with a predictable and clinically manageable increase in hyperkalaemia[1]



Despite the clinical evidence, the **perceived risk** of hyperkalaemia may remain a concern to clinicians

Aim: Develop an easy-to-implement risk model for incident hyperkalaemia in patients with CKD and T2D and analyse the efficacy and safety of finerenone across patients with varying levels of hyperkalaemia risk

*N=6381; #N=6355; ‡laboratory measurement; § investigator-reported AEs using the MedDRA preferred terms 'hyperkalaemia' and 'blood potassium increased'
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TE, treatment-emergent

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

Using the FIDELITY dataset, a risk score model was developed and validated for new-onset hyperkalaemia in patients with CKD and T2D

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Model derivation and validation

- Cox models with stepwise selection used to identify the variables **independently associated with hyperkalaemia***
- Data from the **placebo arm** used for **derivation**, and from the **finerenone arm** for **validation**, of the risk score
- An **integer risk score** was built based on the beta-coefficients of the variables retained in the final model
- Scores were divided based on tertiles into **low (0–3 points), intermediate (4–6 points)** and **high (7–12 points) hyperkalaemia risk categories**
- A stratified Cox proportional hazards model was used to calculate the **treatment effect of finerenone vs placebo** for the primary outcome **in each hyperkalaemia risk category**
- The efficacy of finerenone was also assessed **across hyperkalaemia risk categories,** according to the composite CV# and kidney outcomes,‡ CV death or HHF, CV death and all-cause mortality

Outcome of interest

Primary outcome:

New-onset hyperkalaemia, defined as a laboratory-confirmed first treatment-emergent serum $[K^+]$ >5.5 mmol/l

*Variables included in the Cox proportional hazards model were age (<65, ≥65 years); sex (male, female); race (Asian, other); body mass index (<30, ≥30 kg/m^2); eGFR (<45, ≥45 ml/min), UACR (≤1000, >1000 mg/g); serum potassium level (≤4.5, >4.5 mmol/l); systolic blood pressure (<130, ≥130 mmHg); medical history of hyperkalaemia (yes/no); haemoglobin (<12, ≥12 g/dl); thiazide diuretic use (yes/no); loop diuretic use (yes/no); beta blocker use (yes/no); and sodium-glucose co-transporter-2 inhibitor use (yes/no); #CV death, non-fatal myocardial infarction, non-fatal stroke or HHF; ‡kidney failure, sustained ≥57% eGFR decrease from baseline or kidney-related death

Baseline characteristics considered in the model

Characteristic	Placebo: Any TE serum [K+] >5.5 mmol/l	
	YES (n=470)	NO (n=5885)
Age, years, mean ± SD	63.7 ± 9.4	64.9 ± 9.7
Sex, female, n (%)	162 (34.5)	1682 (28.6)
Race, n (%)		
Asian	108 (23.0)	1320 (22.4)
Black/African American	15 (3.2)	248 (4.2)
White	312 (66.4)	4005 (68.1)
Other*	35 (7.4)	312 (5.3)
SBP, mm Hg, mean ± SD	136.2 ± 13.5	136.8 ± 14.3
Serum [K+] , mmol/l, mean ± SD	4.6 ± 0.4	4.3 ± 0.4
eGFR, ml/min/1.73 m², mean ± SD	51.8 ± 20.4	58.2 ± 21.8
eGFR category, ml/min/1.73 m², n (%)		
<25	11 (2.3)	65 (1.1)
25–<45	198 (42.1)	1859 (31.6)
45–<60	123 (26.2)	1557 (26.5)
≥60		

Characteristic	Placebo: Any TE serum [K+] >5.5 mmol/l	
	YES (n=470)	NO (n=5885)
UACR, mg/g, median (Q1–Q3)	757.68 (269.9–1559.8)	507.33 (195.6–1124.6)
UACR category, mg/g, n (%)		
<30	6 (1.3)	94 (1.6)
30–<300	121 (25.7)	1850 (31.4)
≥300	343 (73.0)	3940 (66.9)
History of hyperkalaemia, n (%)	19 (4.0)	86 (1.5)
BMI, kg/m², mean ± SD	30.5 ± 5.6	31.3 ± 6.0

Baseline medications, n (%)*	Placebo: Any TE serum [K+] >5.5 mmol/l	
	YES (n=470)	NO (n=5885)
Beta blockers	241 (51.3)	2954 (50.2)
Thiazide diuretics	76 (16.2%)	1434 (24.4%)
Loop diuretics	98 (20.9%)	1282 (21.8%)
SGLT-2i	13 (2.8)	419 (7.1)

Patients who **experienced TE serum [K+] >5.5 mmol/l** had **higher baseline serum [K+] and lower baseline eGFR values**

*Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, not reported, and multiple (patients who reported that they belong to more than one race); #multiple drug groups per drug are possible. Therefore, the same drug may be counted in more than one category for the same subject. Medications taken on or before day of randomisation and ended after randomisation are included in this table. BMI, body mass index; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Seven baseline variables were identified as independently associated with new-onset hyperkalaemia*

Derivation of risk score using SAS data from the placebo treatment arm of FIDELITY

Baseline covariate	Category	n/N (n/100 PY)	β-coefficient	HR (95%CI)	*p*-value (Wald)	Integer points
Serum potassium (mmol/l)	≤4.5	192/4400 (1.7)	1.21	1	<0.0001	0
	>4.5	278/1942 (6.1)		3.35 (2.78–4.03)		3
Hyperkalaemia (medical history)	No	451/6237 (2.8)	0.65	1	0.0061	0
	Yes	19/105 (8.3)		1.91 (1.20–3.04)		2
SGLT-2i use	No	457/5911 (3.0)	0.65	1.91 (1.10–3.33)	0.0217	2
	Yes	13/431 (1.1)		1		0
UACR (mg/g)	≤1000	277/4465 (2.3)	0.55	1	<0.0001	0
	>1000	193/1877 (4.7)		1.74 (1.43–2.12)		2
Haemoglobin (g/dl)	<12	150/1352 (5.0)	0.41	1.50 (1.23–1.83)	<0.0001	1
	≥12	320/4990 (2.4)		1		0
Thiazide use	No	394/4838 (3.2)	0.40	1.49 (1.17–1.91)	0.0015	1
	Yes	76/1504 (1.9)		1		0
eGFR (ml/min/1.73 m²)	<45	209/2131 (4.4)	0.30	1.35 (1.10–1.66)	0.0041	1
	≥45	261/4211 (2.3)		1		0

*Lo
CI,

The derivation and validation of the risk score was well calibrated across TE hyperkalaemia risk at 2 years

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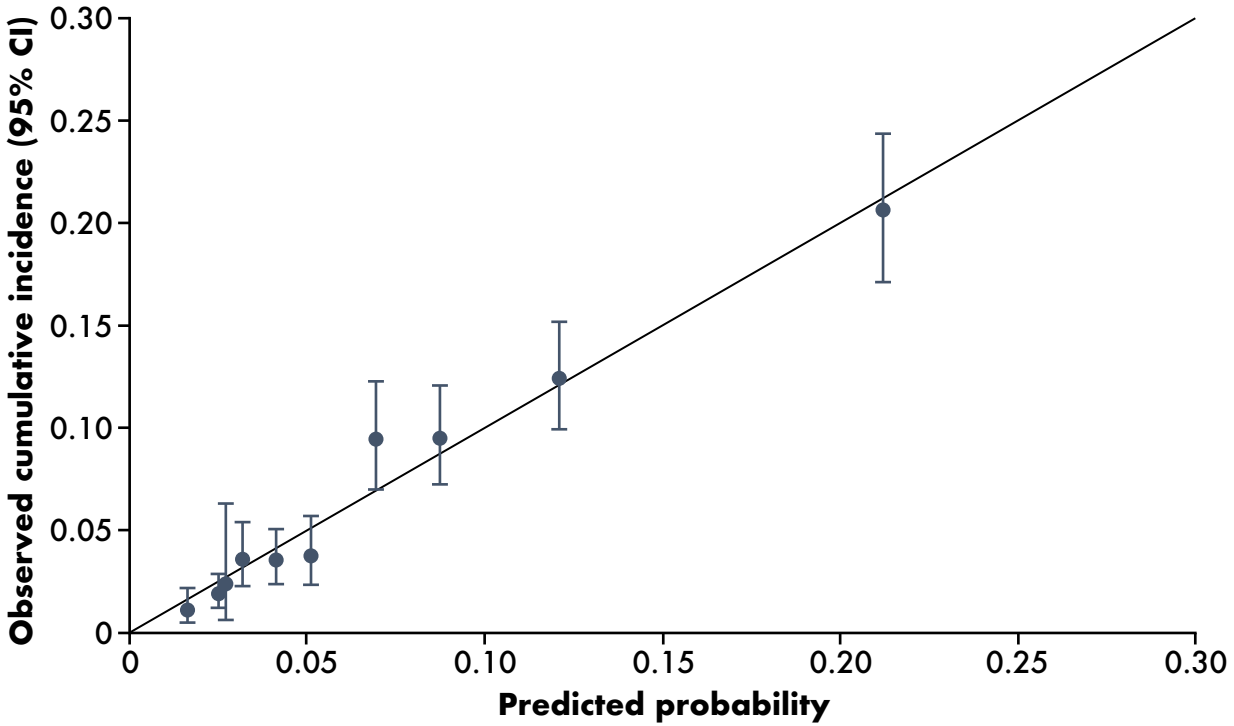
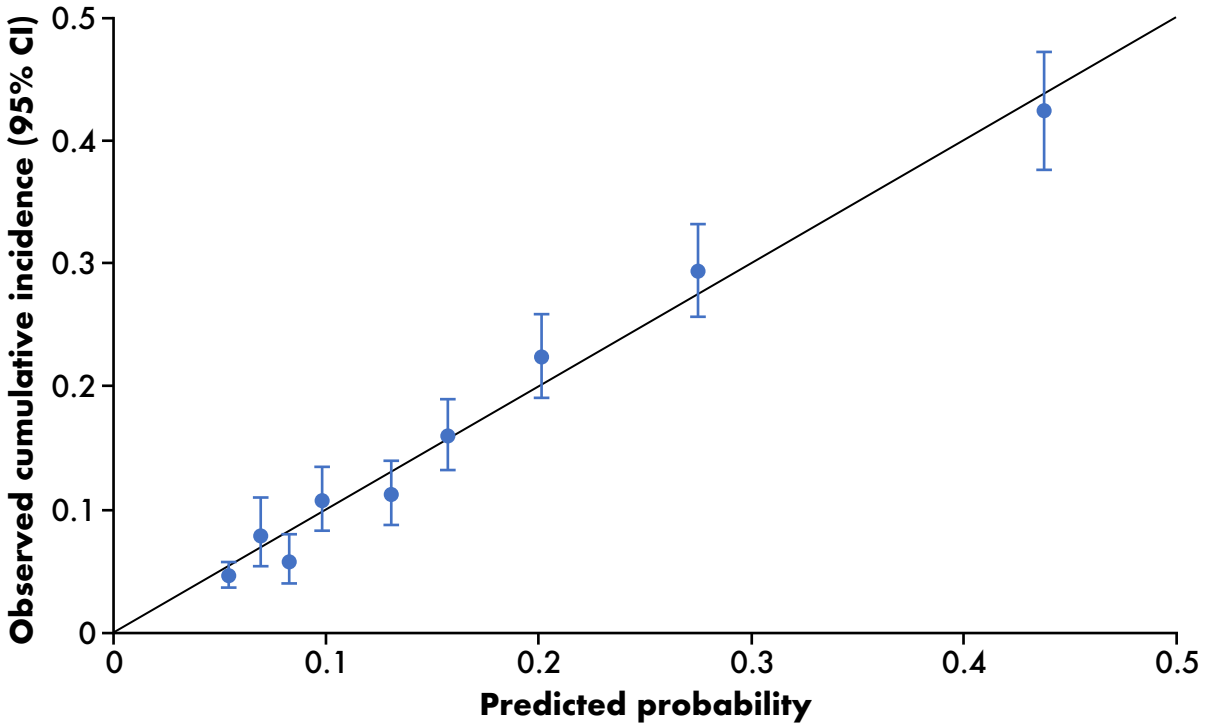
Derivation of risk score using data based on the SAS from the placebo treatment arm of FIDELITY



C-index of the **derivation** model =
0.732 (SE, 0.012)

Validation of risk score using data based on the SAS from the finerenone treatment arm of FIDELITY

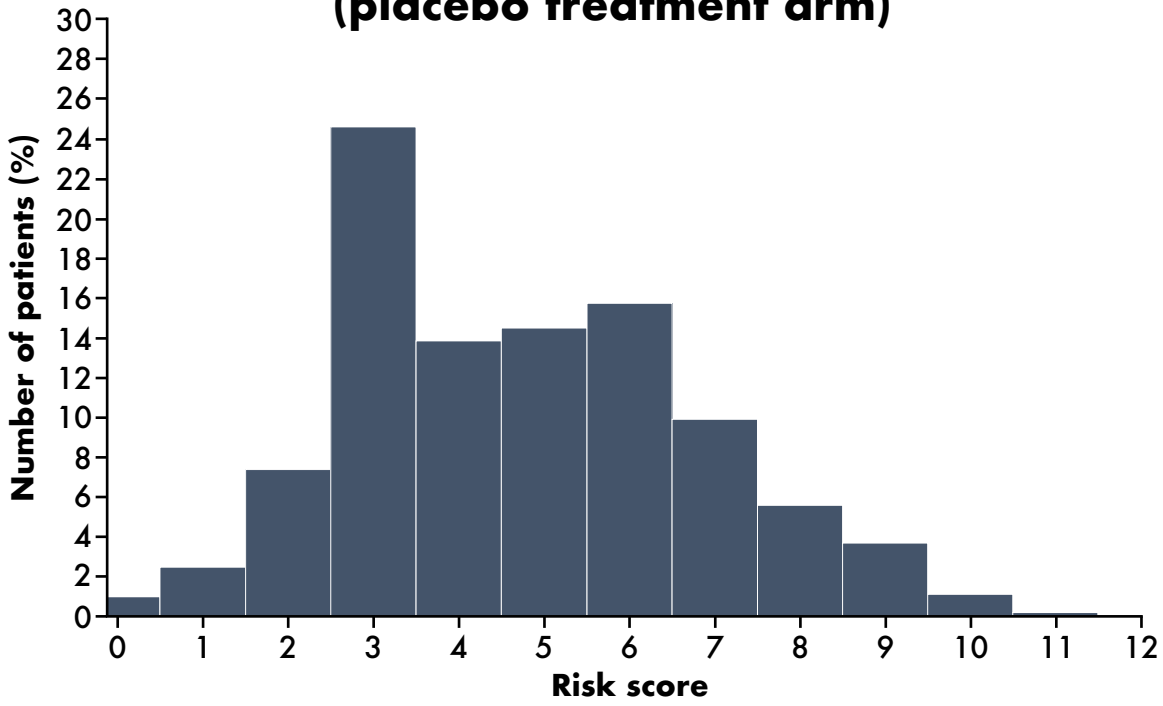


C-index of the **validation** model =
0.721 (SE, 0.008)

SE, standard error

The tertile distributions of the integer risk scores were similar for the derivation and validation models

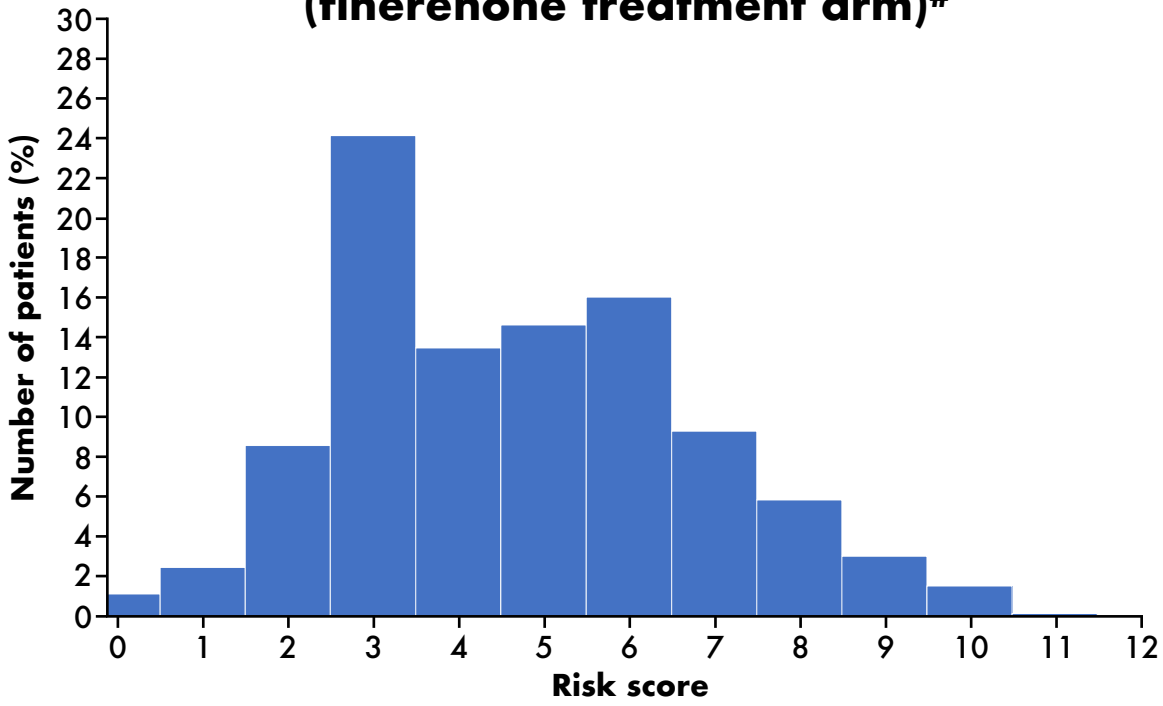
Derivation of risk score (placebo treatment arm)*



- **T1** (low risk; 0–3 points, n=2288 [35.3%])
- **T2** (intermediate risk; 4–6 points, n=2853 [44.1%])
- **T3** (high risk; 7–12 points, n=1327 [20.5%])

Mean ± SD=4.7 ± 2.1 points

Validation of risk score (finerenone treatment arm)#



- **T1** (low risk; 0–3 points, n=2344 [36.1%])
- **T2** (intermediate risk; 4–6 points, n=2854 [44.0%])
- **T3** (high risk; 7–12 points, n=1278 [19.7%])

Mean ± SD=4.7 ± 2.1 points

*Data based on the safety analysis set from the placebo treatment arm of FIDELITY; #data based on the safety analysis set from the finerenone treatment arm of FIDELITY
T, tertile

The risk of TE serum [K^+] >5.5 mmol/l increased in a stepwise manner across hyperkalaemia risk categories in both treatment arms*,#

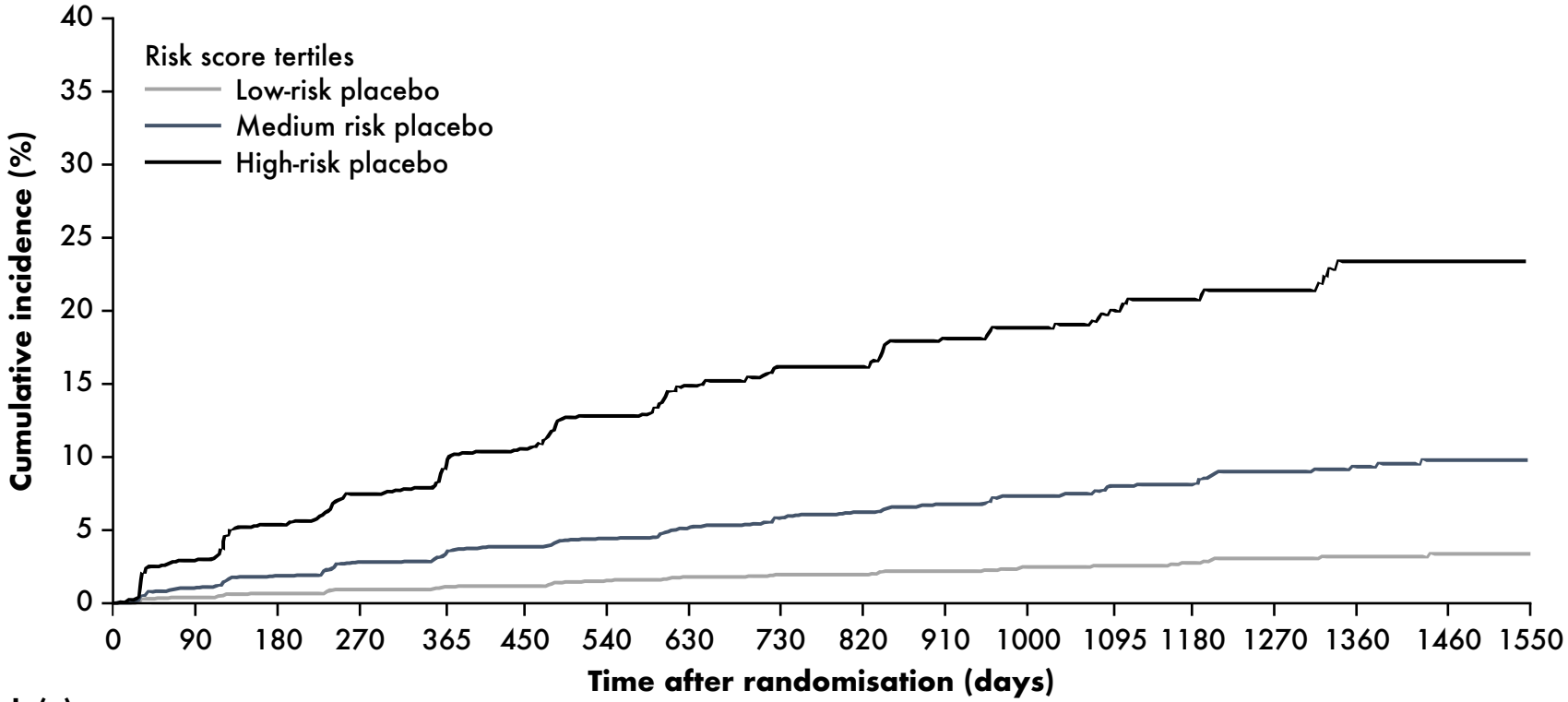
Risk score	Finerenone		Placebo		HR (95% CI)	*p*-value for interaction
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
Overall	1072/6381 (16.8)	7.0	470/6355 (7.4)	2.9	2.45 (2.20–2.73)	–
T1 (low risk)	161/2315 (7.0)	2.5	61/2267 (2.7)	0.9	2.58 (1.92–3.49)	0.38
T2 (intermediate risk)	493/2818 (17.5)	7.6	196/2808 (7.0)	2.8	2.73 (2.31–3.23)	
T3 (high risk)	412/1235 (33.4)	18.7	213/1276 (16.7)	8.0	2.26 (1.91–2.67)	

The relative **increased hyperkalaemia risk** of **finerenone vs placebo** was **similar regardless of the hyperkalaemia risk category**

*Data are based on the safety analysis set of FIDELITY; #patients at risk must have both a baseline and post-baseline TE serum [K^+] value, and the baseline value must be ≤5.5 mmol/l

Risk categories show clear separation of hyperkalaemia risk over time

Cumulative incidence for time to first treatment-emergent serum potassium value >5.5 mmol/l by hyperkalaemia risk categories*,#



Patients at risk (n)

Low-risk placebo	2267	2236	2185	2135	2099	2059	2007	1915	1792	1633	1449	1246	1068	942	805	647	452	326
Medium risk placebo	2808	2723	2622	2520	2443	2372	2272	2101	1846	1631	1393	1176	958	809	638	460	283	175
High-risk placebo	1276	1196	1135	1073	1007	951	871	771	647	564	462	385	303	240	181	123	58	41

*Aalen-Johansen estimates are displayed; #patients at risk are from the placebo treatment arm and must have both a baseline and post-baseline TE serum $[K^+]$ value, while the baseline value must be ≤5.5 mmol/l

Overall, finerenone reduced the incidence of CV and kidney events versus placebo, regardless of hyperkalaemia risk category

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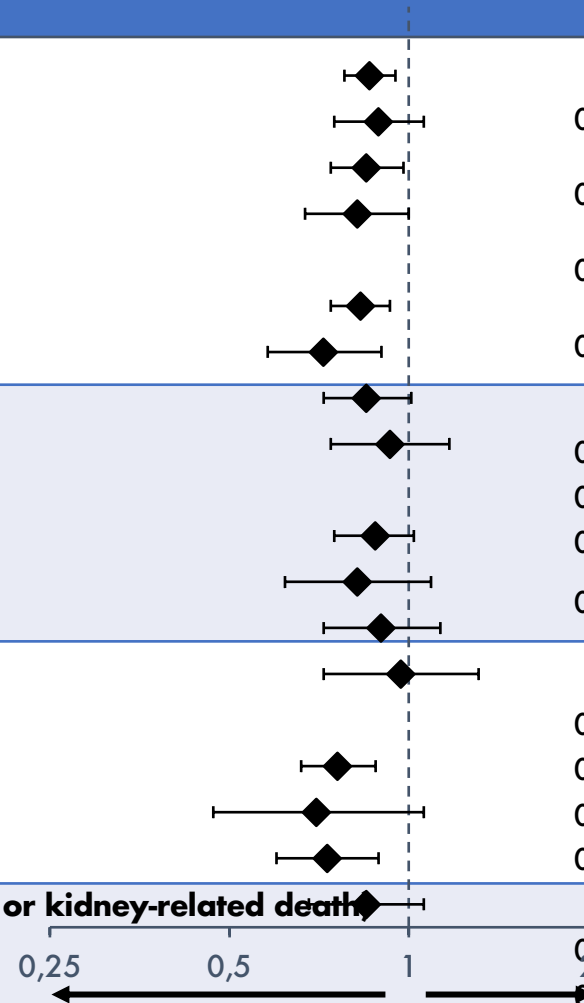
	Finerenone		Placebo		Hazard ratio (95% CI)	p-value for interaction
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
Composite CV outcome (CV death, non-fatal MI, non-fatal stroke or HHF)						
Overall	823/6498 (12.7)	4.3	938/6492 (14.4)	5.0	0.86 (0.78–0.95)	
T1 (low risk)	246/2345 (10.5)	3.3	261/2292 (11.4)	3.6	0.89 (0.75–1.06)	0.7221
T2 (intermediate risk)	384/2856 (13.4)	4.8	443/2858 (15.5)	5.5	0.85 (0.74–0.98)	
T3 (high risk)	187/1283 (14.6)	5.5	232/1335 (17.4)	6.8	0.82 (0.67–1.00)	
CV death or HHF						
Overall	537/6498 (8.3)	2.8	640/6492 (9.9)	3.3	0.83 (0.74–0.93)	
T1 (low risk)	139/2345 (5.9)	1.8	181/2292 (7.9)	2.5	0.72 (0.58–0.90)	0.3849
T2 (intermediate risk)	249/2856 (8.7)	3.0	291/2858 (10.2)	3.5	0.85 (0.72–1.01)	
T3 (high risk)	144/1283 (11.2)	4.2	166/1335 (12.4)	4.7	0.93 (0.74–1.17)	
CV death						
Overall	321/6498 (4.9)	1.6	364/6492 (5.6)	1.8	0.88 (0.75–1.02)	
T1 (low risk)	90/2345 (3.8)	1.2	106/2292 (4.6)	1.4	0.82 (0.62–1.09)	0.8298
T2 (intermediate risk)	143/2856 (5.0)	1.7	160/2858 (5.6)	1.9	0.90 (0.72–1.13)	
T3 (high risk)	86/1283 (6.7)	2.4	96/1335 (7.2)	2.6	0.97 (0.72–1.31)	
Composite kidney outcome (kidney failure, sustained ≥57% eGFR decrease from baseline or kidney-related death)						
Overall	356/6498 (5.5)	2.0	465/6492 (7.2)	2.6	0.76 (0.66–0.88)	
T1 (low risk)	41/2345 (1.7)	0.6	56/2292 (2.4)	0.8	0.70 (0.47–1.06)	0.4924
T2 (intermediate risk)	175/2856 (6.1)	2.3	233/2858 (8.2)	3.0	0.73 (0.60–0.89)	

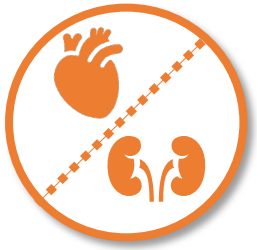


Data based on the full analysis set of FIDELITY

Summary

Using data from the FIDELITY pooled analysis,[1] an **easy-to-use integer risk score for new-onset hyperkalaemia** was developed and validated **for patients with CKD and T2D**

Efficacy outcome analyses demonstrated that **finerenone lowered the risk of CV and kidney events** versus placebo in **patients with CKD and T2D across different hyperkalaemia risk categories**



This risk score model could be **useful in clinical practice** for risk stratification of hyperkalaemia in individual patients, particularly for those at high risk, and could aid in **tailored disease management and follow up**

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

Thank you

Executive committee

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

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FIDELITY

FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme anaLYsis

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