Finerenone in patients with CKD, T2D and anaemia: A FIDELITY analysis

This FIDELITY post hoc analysis investigated the efficacy and safety of finerenone versus placebo by baseline anaemia status

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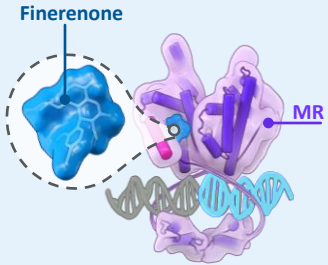
Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company : Bayer, GSK, Zydus, Nephrology Times, and Chinook

Finerenone is a selective, nonsteroidal MRA that has demonstrated CV and kidney benefits in patients with CKD and T2D



Finerenone is a **nonsteroidal MRA that selectively blocks MR overactivation**. MR overactivation is thought to contribute to CV and kidney disease progression[1,2]

FIDELIO-DKD[3] (N=5674*) + **FIGARO**-DKD[4] (N=7352*) = **FIDELITY**[1] (N=13,026*)

Eligibility criteria:

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

In FIDELITY, **finerenone significantly reduced risk of CV outcomes** and **slowed CKD progression** versus placebo in patients with CKD and T2D[5]

14% reduced **risk of CV morbidity and mortality**[#] (HR=0.86; 95% CI 0.78–0.95; *p*=0.0018)

23% reduced **risk of CKD progression**[‡] (HR=0.77; 95% CI 0.67–0.88; *p*=0.0002)

*Patients analysed; [#]CV composite outcome of time to CV death, non-fatal MI, non-fatal stroke or HHF; [‡]kidney composite outcome of time to kidney failure, sustained ≥57% decrease in eGFR from baseline or kidney death
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; HR, hazard ratio; [K^+], potassium concentration; MI, myocardial infarction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; T2D, type 2 diabetes

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Agarwal R, *et al. Nephrol Dial Transplant* 2022;37:1014–1023; 3. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 4. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

Observational studies have associated anaemia with heightened risk of adverse heart and kidney outcomes and mortality in patients with CKD[1]

Anaemia is defined by the WHO as[2]:

♀ Hb <12 g/dl ♂ Hb <13 g/dl

Moderate–severe anaemia:
Hb ≤10 g/dl

Anaemia is a common complication in **patients with CKD and diabetes**[3,4]

Prevalence ↑ as eGFR ↓

The **aetiology of anaemia** in CKD is multifactorial[5]

- **Erythropoietin deficiency**
- **Disordered iron homeostasis**
- **Inflammation**

Analysis objective: Anaemia is a risk factor for adverse CV outcomes in patients with CKD. The purpose of this study was to investigate the effect of finerenone on patients with anaemia versus patients without anaemia

Hypothesis: Baseline anaemia status does not modify the effect of finerenone on cardiovascular and kidney protection, but may be a potential marker for more severe disease

Hb, haemoglobin; WHO, World Health Organization. 1. Babitt JL & Lin HY. *J Am Soc Nephrol* 2012;23:1631–1634; 2. World Health Organization (WHO). 2011. https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1 [accessed 13 Jun 2023]; 3. Vestergaard SV, *et al. Clin Epidemiol* 2020;12:953–962; 4. Fishbane S & Spinowitz B. *Am J Kidney Dis* 2018;71:423–435; 5. Lamerato L, *et al. BMC Nephrol* 2022;23:166.

Key outcomes were stratified by baseline anaemia status

Key outcomes

Primary:

CV composite: Time to CV death, non-fatal MI, non-fatal stroke or HHF

Kidney composite: Time to kidney failure, sustained ≥57% decrease in eGFR from baseline, or kidney death

HHF

All-cause mortality

Secondary kidney composite*

Safety: AEs, including hyperkalaemia

Statistical analysis

- **Time-to-event analyses of clinical outcomes** were conducted using stratified Cox proportional hazards models[#]
- In a **sensitivity analysis, anaemia status over time** (from baseline to end of study) and the **relationship to efficacy outcomes** were investigated with time-dependent Cox proportional hazards models[#‡]
- To account for possible **non-linear effects of Hb level on clinical outcomes, Hb was modelled using cubic splines** with three knots in the stratified Cox proportional hazards models

*Time to kidney failure, sustained ≥40% decrease in eGFR from baseline over ≥4 weeks or kidney death; [#]stratification factors: geographic region, eGFR and UACR categories at screening, history of CV disease and study; [‡]additional stratification factors: treatment (finerenone or placebo), anaemia status as a time-dependent covariate and its interaction with treatment. AE, adverse event; UACR, urine albumin-to-creatinine ratio

Baseline characteristics by anaemia status

Approximately one-third of patients analysed had anaemia*

Patient characteristics	Anaemia (n=4293)	No anaemia (n=8714)
Age, years, mean	65.5	64.4
Sex, female, %	33.6	28.6
Race and ethnicity, %		
Asian	26.6	20.1
Black/African American	7.0	2.5
White	59.9	72.1
SBP/DBP, mmHg, mean	137/73	137/78
Duration of diabetes, years, mean	17.0	14.6
HbA1c, %, mean	7.6	7.8
Laboratory parameters at baseline		
Serum potassium, mmol/l, mean	4.4	4.3
hs-CRP, mg/l, mean	5.5	4.4
eGFR, ml/min/1.73 m^2, mean	49.3	61.7
UACR, mg/g, median	582.4	487.3

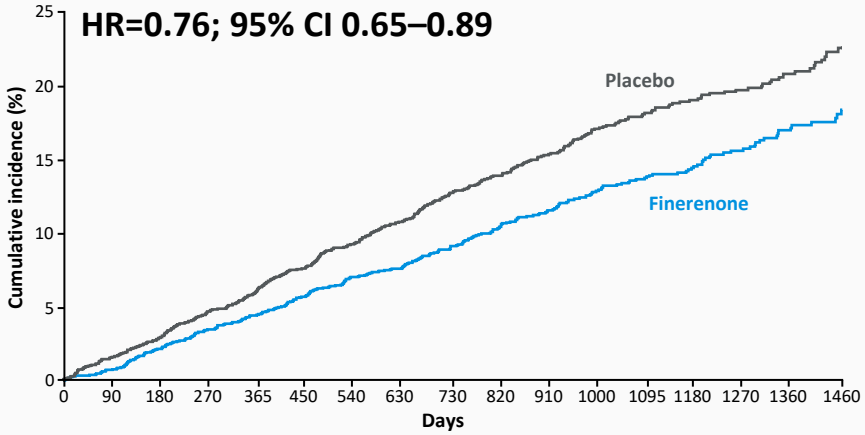
Patient characteristics	Anaemia (n=4293)	No anaemia (n=8714)
Medical History, %		
CV disease	48.3	44.2
Heart failure	8.9	7.6
Atrial fibrillation or flutter	7.1	8.8
Medications, %		
CV medications		
RASi	99.8	99.9
Statins	75.0	70.8
Diuretics	56.0	49.4
Beta blockers	51.2	49.3
Calcium channel blockers	60.7	54.4
Erythropoietin stimulating agents	2.0	0
≥1 glucose-lowering therapy		
Insulin	62.1	56.8
GLP-1RA	6.4	7.7
SGLT-2i	3.0	8.6

*Anaemia defined as <12 g/dl for female and <13 g/dl for male and <10 g/dl as moderate–severe anaemia

DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Finerenone was associated with a lower risk of the CV composite outcome* versus placebo in patients with anaemia

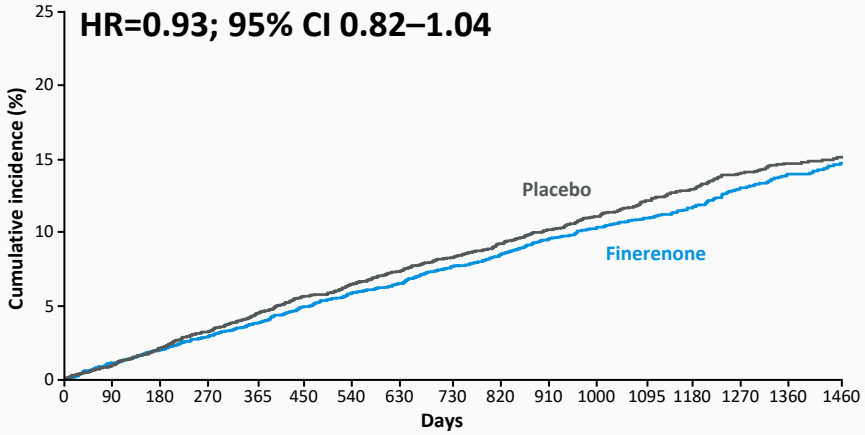
Anaemia at baseline



Number of patients at risk

Finerenone	2125	2106	2064	2031	2000	1966	1925	1796	1617	1455	1259	1051	876	758	610	426	263
Placebo	2168	2130	2091	2045	2009	1973	1929	1788	1615	1446	1254	1032	865	731	597	438	259

No anaemia at baseline



Number of patients at risk

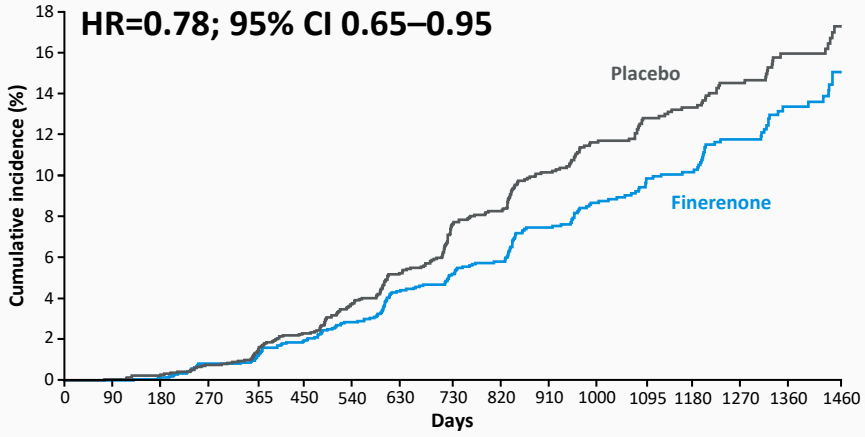
Finerenone	4381	4327	4283	4238	4191	4140	4073	3928	3646	3324	2939	2572	2184	1882	1573	1236	822
Placebo	4333	4286	4233	4173	4110	4051	4003	3843	3564	3261	2890	2491	2102	1820	1536	1180	822

The overall effect of finerenone on the CV composite outcome was significantly greater in patients with anaemia at baseline versus those without ($p_{interaction}$=0.04)

*Time to CV death, non-fatal MI, non-fatal stroke or HHF

A reduced risk of the ≥57% eGFR composite kidney outcome* was observed with finerenone versus placebo in patients with and without anaemia

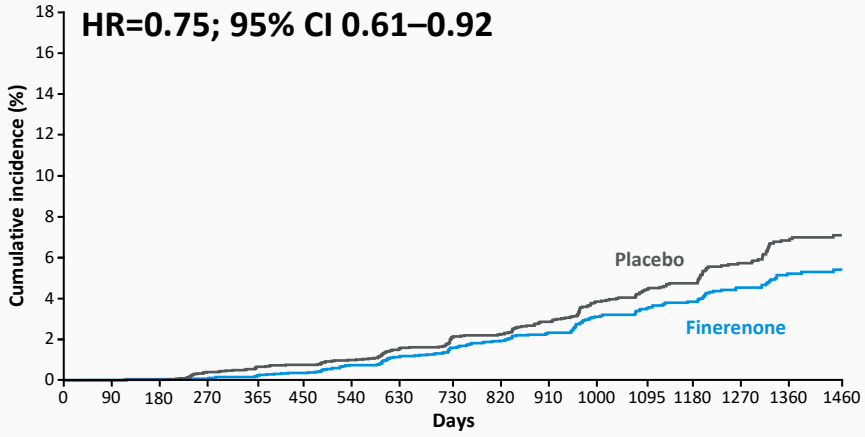
Anaemia at baseline



Number of patients at risk

Finerenone	2125	2087	2032	1983	1949	1897	1831	1680	1497	1342	1138	947	772	676	532	362	211
Placebo	2168	2120	2077	2026	1978	1936	1853	1697	1496	1344	1139	948	793	673	541	392	220

No anaemia at baseline



Number of patients at risk

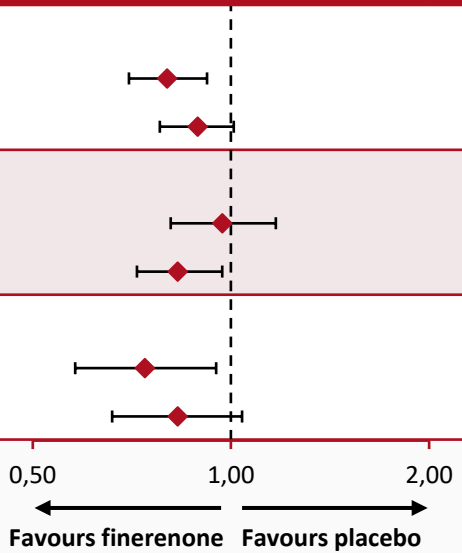
Finerenone	4381	4314	4248	4195	4147	4096	4007	3820	3520	3208	2825	2416	2037	1782	1488	1147	747
Placebo	4333	4276	4210	4134	4088	4042	3957	3767	3449	3187	2790	2379	2003	1745	1446	1092	741

The treatment effect of finerenone on the ≥57% eGFR composite kidney outcome was not modified by baseline anaemia status ($p_{interaction}$=0.85)

*Time to kidney failure, sustained ≥57% decrease in eGFR from baseline, or kidney-related death

The effect of finerenone on the ≥40% eGFR kidney composite outcome, all-cause mortality and HHF was not modified by baseline anaemia status

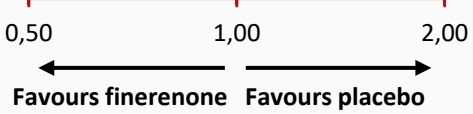
Endpoint	Finerenone		Placebo		HR (95% CI)	$p_{interaction}$
	n/N	n/100 PY	n/N	n/100 PY		
≥40% eGFR kidney composite outcome						
With anaemia	391/2084	7.54	493/2125	9.41	0.80 (0.70–0.92)	0.24
Without anaemia	447/4381	3.60	490/4333	3.98	0.89 (0.78–1.01)	
All-cause mortality						
With anaemia	229/2084	3.79	237/2125	3.83	0.97 (0.81–1.17)	0.18
Without anaemia	315/4381	2.29	372/4333	2.75	0.83 (0.72–0.97)	
HHF						
With anaemia	110/2084	1.87	155/2125	2.60	0.74 (0.58–0.95)	0.47
Without anaemia	140/4381	1.04	164/4333	1.24	0.83 (0.66–1.04)	



PY, patient-years

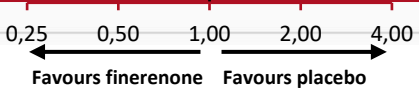
The effect of finerenone on all outcomes was not modified by anaemia status when assessed as a time-dependent variable

Endpoint	HR (95% CI)	$p_{interaction}$
CV composite outcome		0.27
With anaemia	0.80 (0.69–0.93)	
Without anaemia	0.89 (0.79–1.01)	
≥57% kidney composite outcome		0.23
With anaemia	0.71 (0.61–0.83)	
Without anaemia	0.88 (0.65–1.21)	
≥40% kidney composite outcome		0.08
With anaemia	0.77 (0.69–0.87)	
Without anaemia	0.92 (0.78–1.09)	
All-cause mortality		0.43
With anaemia	0.92 (0.78–1.09)	
Without anaemia	0.84 (0.71–0.99)	

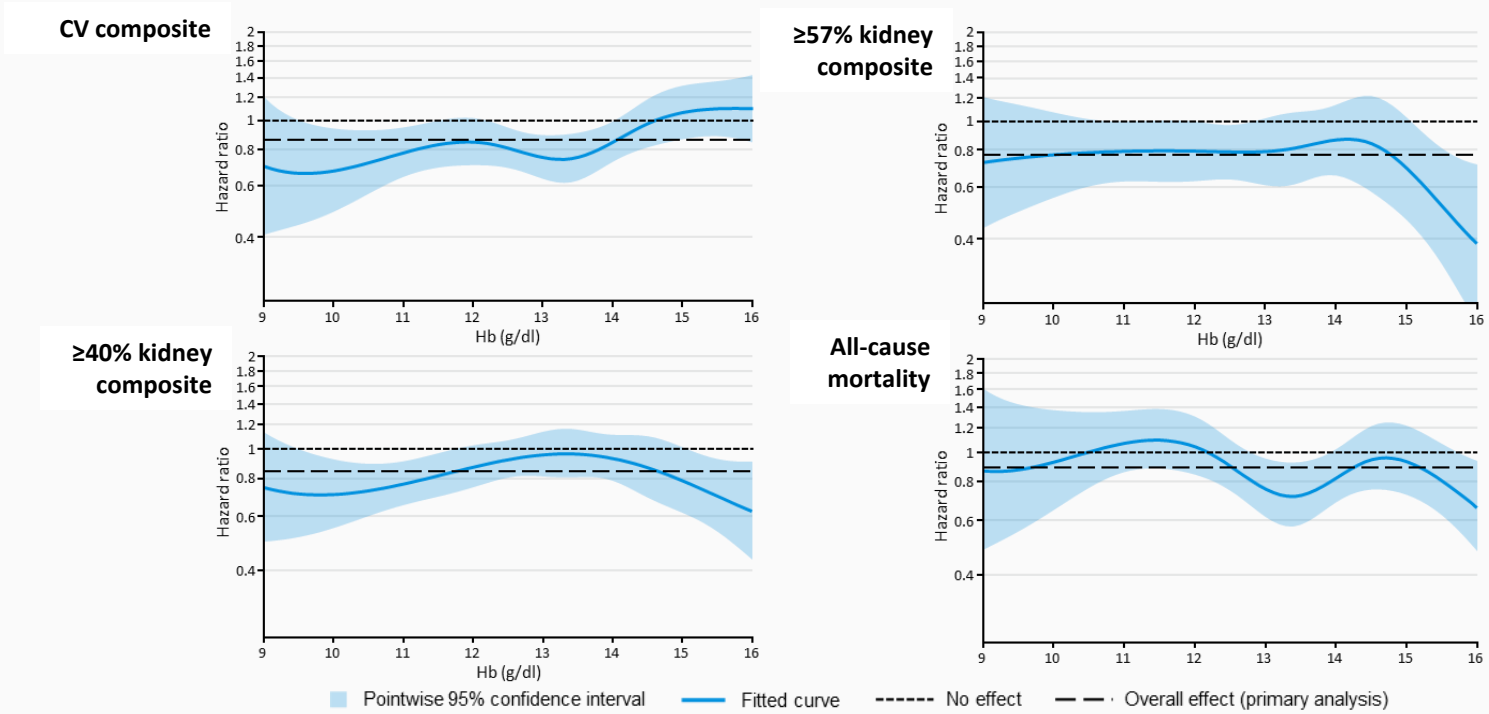


The benefit of finerenone was observed irrespective of severity of anaemia

Endpoint	Finerenone		Placebo		HR (95% CI)	$p_{interaction}$
	n/N	n/100 PY	n/N	n/100 PY		
CV composite outcome						
With anaemia	266/1967	4.87	360/1999	6.61	0.74 (0.63–0.87)	0.09
With moderate–severe anaemia	29/152	7.43	32/164	7.84	0.94 (0.53–1.66)	
Without anaemia	524/4387	3.99	546/4338	4.24	0.93 (0.82–1.05)	
≥57% kidney composite outcome						
With anaemia	172/1967	3.34	215/1999	4.1	0.82 (0.67–1.01)	0.62
With moderate–severe anaemia	25/152	6.8	42/164	11.67	0.67 (0.38–1.18)	
Without anaemia	163/4387	1.28	208/4338	1.65	0.76 (0.62–0.93)	
≥40% kidney composite outcome						
With anaemia	364/1967	7.39	448/1999	8.98	0.82 (0.72–0.95)	0.42
With moderate–severe anaemia	40/152	11.67	57/164	16.91	0.67 (0.42–1.07)	
Without anaemia	450/4387	3.62	490/4338	3.98	0.89 (0.79–1.02)	
All-cause mortality						
With anaemia	209/1967	3.65	216/1999	3.69	0.98 (0.81–1.18)	0.38
With moderate–severe anaemia	25/152	5.92	24/164	5.39	1.13 (0.59–2.16)	
Without anaemia	315/4387	2.29	372/4338	2.75	0.83 (0.72–0.97)	
HHF						
With anaemia	97/1967	1.74	151/1999	2.69	0.67 (0.51–0.86)	0.09
With moderate–severe anaemia	15/152	3.76	10/164	2.34	1.36 (0.55–3.36)	
Without anaemia	141/4387	1.04	164/4338	1.24	0.84 (0.67–1.05)	



The benefit of finerenone on CV and kidney composite outcomes was observed across a broad range of Hb levels



Patients with anaemia experienced a higher number of AEs, including hyperkalaemia, versus patients without anaemia for both the finerenone and placebo treatment arms

n (%)	Anaemia		No anaemia	
	Finerenone (n=2123)	Placebo (n=2156)	Finerenone (n=4375)	Placebo (n=4328)
Any AE (%)	1865 (87.8)	1916 (88.9)	3727 (85.2)	3687 (85.2)
Related to study drug	521 (24.5)	353 (16.4)	682 (15.6)	509 (11.8)
Leading to discontinuation	178 (8.4)	161 (7.5)	236 (5.4)	189 (4.4)
Any serious AE	764 (36.0)	824 (38.2)	1291 (29.5)	1360 (31.4)
Related to study drug	44 (2.1)	29 (1.3)	38 (0.9)	32 (0.7)
Leading to discontinuation	69 (3.3)	67 (3.1)	76 (1.7)	86 (2.0)
Any AE leading to death	52 (2.4)	49 (2.3)	58 (1.3)	102 (2.4)
Any investigator-reported hyperkalaemia	501 (23.6)	306 (14.2)	496 (11.3)	245 (5.7)
Any treatment-emergent event	451 (21.2)	249 (11.5)	459 (10.5)	199 (4.6)
Leading to permanent discontinuation	55 (2.6)	25 (1.2)	55 (1.3)	13 (0.3)
Classified as a serious AE	42 (2.0)	13 (0.6)	26 (0.6)	3 (<0.1)
Leading to hospitalisation	36 (1.7)	7 (0.3)	24 (0.5)	3 (<0.1)
Leading to death	0	0	0	0
Serum potassium >5.5 mmol/l, (Num/Den, %)*	512/2083 (24.6)	207/2113 (9.8)	557/4307 (12.9)	263/4254 (6.2)

The number of AEs was highest in patients with moderate–severe anaemia compared to patients with mild–moderate anaemia or no anaemia

*Num/Den, number/denominator

Summary

In FIDELITY, one-third **of patients had anaemia at baseline, having more advanced CKD** and **a higher number of comorbidities** than those without anaemia

The **risk of the CV composite outcome** in patients with anaemia **was significantly reduced with finerenone** versus those without

The risk of the **kidney composite outcome** and **HHF were lower with finerenone** versus placebo, irrespective of baseline anaemia status

Treatment-emergent AEs were mostly **balanced between the treatment arms,** but **patients with anaemia** experienced a **higher number of AEs** (including hyperkalaemia) than patients without anaemia, likely due to having more severe disease at baseline

Limitations of this analysis include:

- **Post hoc** analysis and small sample size
- Presence of anaemia representing a **marker of severity of heart and kidney disease**
- Several **anaemia-related variables not being measured** in the trials

The **cardioprotective** effect of finerenone observed in FIDELITY is likely to be **preserved and more pronounced in patients with anaemia** versus those without anaemia

Anaemia could be a **marker for high-risk patients** who may gain **greater heart and kidney benefit with finerenone**