Finerenone and canagliflozin in the treatment of chronic kidney disease and type 2 diabetes: Matching-adjusted indirect treatment comparison of FIDELIO-DKD and CREDENCE

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Cardiorenal efficacy of finerenone and canagliflozin in patients with CKD and T2D on top of RAS blockade

FIDELIO-DKD[1]

Endpoint	HR (95% CI)	*P* value
Primary composite outcome of kidney failure,* **sustained eGFR decrease ≥40% from baseline** or death from kidney disease	0.82 (0.73–0.93)	0.001
Secondary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure	0.86 (0.75–0.99)	0.03

CREDENCE[2]

Endpoint	HR (95% CI)	*P* value
Primary composite outcome of end-stage kidney disease,* doubling of serum creatinine (**equivalent to eGFR decrease of 57% from baseline**) or death from kidney disease or CVD	0.70 (0.59–0.82)	0.00001

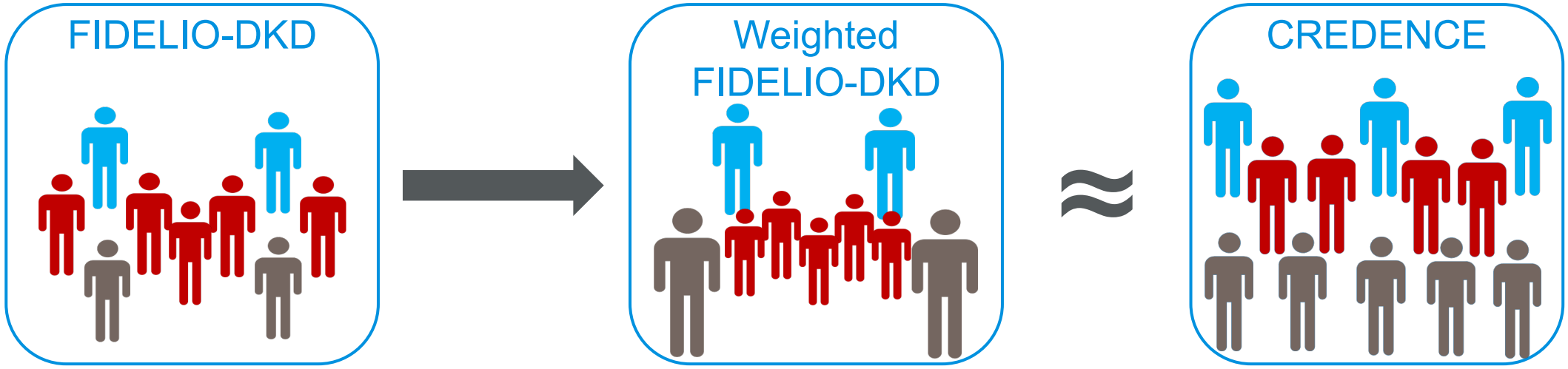
To enable comparison between finerenone and canagliflozin, differences in the study populations and primary outcomes (e.g., eGFR decrease from baseline of ≥40% in FIDELIO-DKD vs 57% in CREDENCE) between the trials need to be accounted for

*The kidney failure endpoint in FIDELIO-DKD is, with minor differences, the same as the endpoint of end-stage kidney disease in CREDENCE. CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAS, renin–angiotensin system; T2D, type 2 diabetes.

1. Bakris GL, et al. *N Engl J Med*. 2020;383:2219–2229. 2. Perkovic V, et al. *N Engl J Med*. 2019;380:2295–2306.

MAIC methodology provides estimates of relative treatment effects after adjusting for between-trial differences in baseline characteristics

1. Select matching variables (baseline characteristics)
2. Assign weights to each patient in FIDELIO-DKD,[1] so the weighted population of FIDELIO-DKD[1] matches that of CREDENCE[2] for eGFR, UACR, history of CVD and BMI at baseline
3. Estimate the finerenone vs placebo HR for the weighted population
4. Estimate the HR comparing finerenone with canagliflozin



BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; UACR, urinary albumin-to-creatinine ratio.

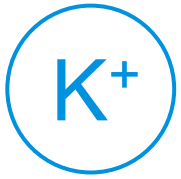
1. Bakris GL, et al. *N Engl J Med*. 2020;383:2219–2229. 2. Perkovic V, et al. *N Engl J Med*. 2019;380:2295–2306.

Objective

- Investigate the relative effects of finerenone and canagliflozin on:

Cardiorenal composite endpoint as assessed in CREDENCE[1]:

– Kidney failure (dialysis, transplantation or sustained eGFR <15 ml/min/1.73 m^2), a doubling of serum creatinine level (equivalent to eGFR decrease of 57% from baseline) or death from kidney disease or CVD



Hyperkalaemia

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

1. Perkovic V, et al. *N Engl J Med*. 2019;380:2295–2306.

No substantial imbalances existed in the post-matching values of the baseline characteristics

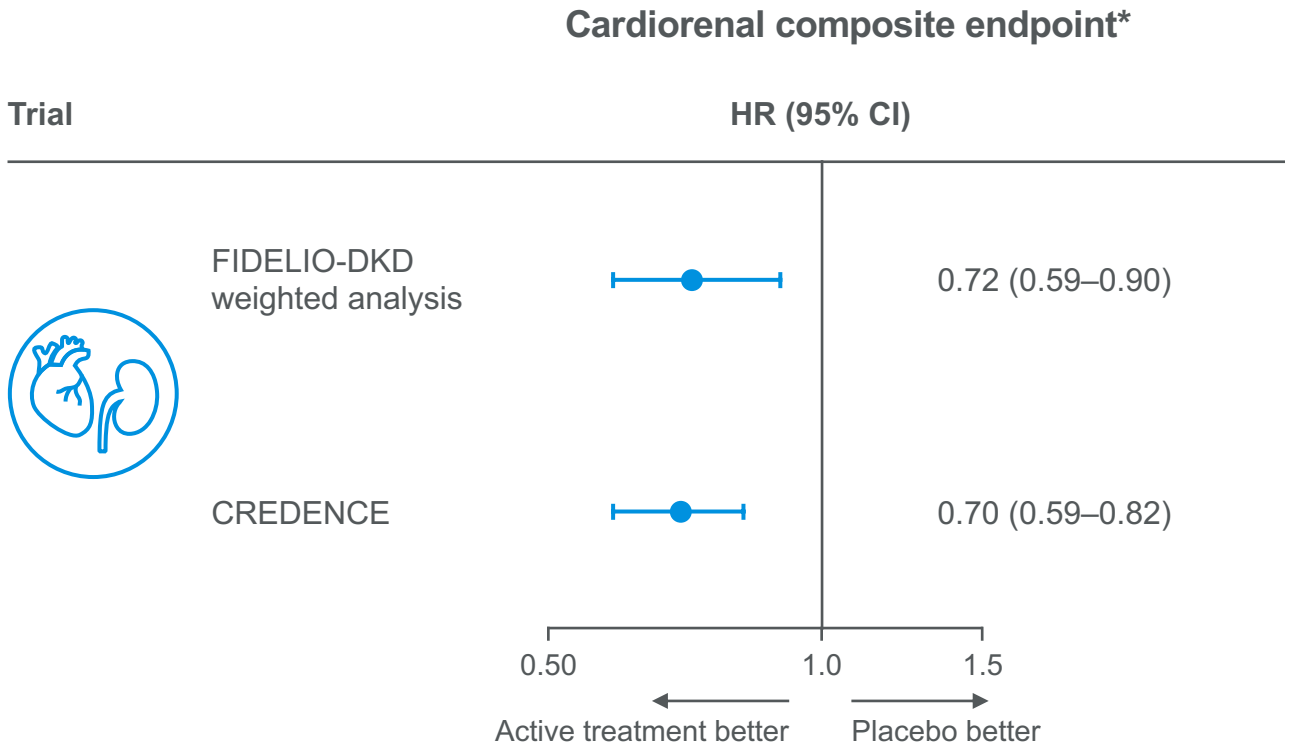
- Applying estimated weights to the FIDELIO-DKD population (N=5674)[1] resulted in an effective sample size of 1288 to compare with the CREDENCE population (N=4401)[2]

Variables included in MAIC analysis	FIDELIO-DKD pre-matching (N=5674)	FIDELIO-DKD post-matching (N=1288)	CREDENCE (N=4401)
eGFR, mean (SD), ml/min/1.73 m²	44.3 (12.6)	56.2 (18.2)	56.2 (18.2)
UACR, % (n)			
≤300 mg/g	12.5 (708)	12.0 (154.5)	12.0 (527)
>300 to ≤3000 mg/g	80.0 (4542)	76.6 (986.5)	76.6 (3371)
>3000 mg/g	7.5 (424)	11.4 (146.8)	11.4 (503)
History of CVD, % (n)			
Yes	45.9 (2605)	50.4 (649.1)	50.4 (2220)
No	54.1 (3069)	49.6 (638.8)	49.6 (2181)
BMI, mean (SD), kg/m²	31.1 (6.0)	31.3 (6.2)	31.3 (6.2)

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MAIC, matching-adjusted indirect comparison; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

1. Bakris GL, et al. *N Engl J Med*. 2020;383:2219–2229. 2. Perkovic V, et al. *N Engl J Med*. 2019;380:2295–2306.

No evidence of a significant difference between finerenone and canagliflozin was found for the cardiorenal composite endpoint



HR for finerenone vs canagliflozin was 1.03 (95% CI 0.79–1.35) *P*=0.802

K+

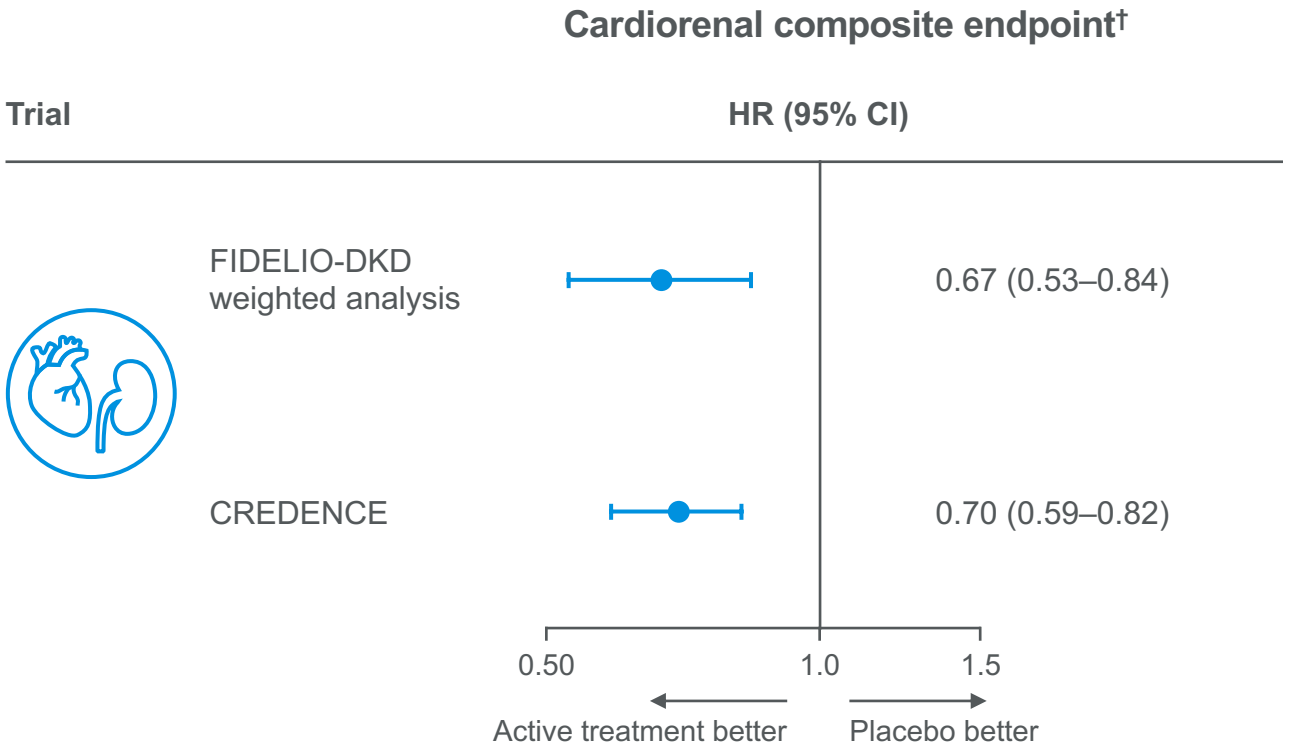
In the absence of more granular data available from CREDENCE, overall hyperkalaemia rates were also analysed. As anticipated, the risk vs placebo remained greater with finerenone after reweighting (HR 1.80 [95% CI 1.46–2.21]) than with canagliflozin vs placebo (HR 0.80 [95% CI 0.65–1.00])

– This translated to a HR for finerenone vs canagliflozin of 2.25 (95% CI 1.67–3.03), *P*<0.001

*Kidney failure (dialysis, transplantation or sustained eGFR <15 ml/min/1.73 m^2), a doubling of serum creatinine level (equivalent to eGFR decrease of 57% from baseline) or death from kidney disease or CVD.[1] CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

1. Perkovic V, et al. *N Engl J Med*. 2019;380:2295–2306.

A sensitivity analysis in a restricted population,* which additionally matched patients based on their heart failure history, showed similar results



HR for finerenone vs canagliflozin was 0.95 (95% CI 0.71–1.27) *P*=0.733

K^+

Similar to the main analysis, the overall hyperkalaemia risk vs placebo remained greater with finerenone after reweighting (HR 1.77 [95% CI 1.40–2.25]) than with canagliflozin (HR 0.80 [95% CI 0.65–1.00])

- This translated to a HR for finerenone vs canagliflozin of 2.22 (95% CI 1.61–3.06), *P*<0.001

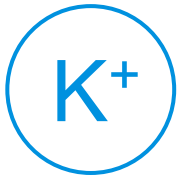
*The effective sample size for this sensitivity analysis was 894. The FIDELIO-DKD population was restricted such that only patients with baseline age, eGFR and UACR within the requirements of CREDENCE were included; patients receiving SGLT2i at baseline were excluded. †Kidney failure (dialysis, transplantation or sustained eGFR <15 ml/min/1.73 m^2), a doubling of serum creatinine level (equivalent to eGFR decrease of 57% from baseline) or death from kidney disease or CVD.[1] CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT2i, sodium–glucose co-transporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

1. Perkovic V, et al. *N Engl J Med*. 2019;380:2295–2306.

Conclusions

- In the absence of head-to-head studies, a MAIC of FIDELIO-DKD and CREDENCE enabled more robust assessment of finerenone and canagliflozin when meaningful differences between studies were accounted for by reweighting patients to minimise population heterogeneity
- The analysis used FIDELIO-DKD individual patient-level data for calculation of the respective endpoints and aggregated data from CREDENCE

Using this payer-accepted methodology,[1] there was no evidence of a significant difference between finerenone and canagliflozin in the cardiorenal composite endpoint as assessed in CREDENCE in patients with CKD and T2D



The anticipated risk of hyperkalaemia with finerenone remained, even after accounting for differences between studies

- These results are consistent with a recent analysis (CREDENCE-like) that used an alternative approach to account for differences between the FIDELIO-DKD and CREDENCE inclusion criteria and endpoints[2]

CKD, chronic kidney disease; MAIC, matching-adjusted indirect comparison; T2D, type 2 diabetes.

1. Phillippo DM, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
2. Agarwal R, et al. *Nephrol Dial Transplant*. 2021; Epub ahead of print.