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Pooled RCTs: In patients with type 2 diabetes and CKD, finerenone improved CV and kidney outcomes

Agarwal R, Filippatos G, Pitt B, et al. **Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis.** Eur Heart J. 2021 Nov 22. pii: 6433104. 35023547

Question

In patients with type 2 diabetes and chronic kidney disease (CKD), what is the effect of adding finerenone vs. placebo to usual care on cardiovascular (CV) events and kidney disease progression?

Design

Individual patient data meta-analysis of 2 randomized placebo-controlled trials (RCTs) (The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis [FIDELITY]).

Blinding

Treatment allocation concealed; blinded (patients, clinicians, pharmacists, and outcome assessors).*

Setting

48 countries.

Patients

13 026 adults aged ≥18 years (mean age, 65 y; 70% men) who had type 2 diabetes and CKD (persistent moderately increased albuminuria, UACR ≥3.39 mg/mmol, and diabetic retinopathy; or severely increased albuminuria, ≥33.9 mg/mmol) treated with a maximum tolerated dose of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Key exclusions: Glycated hemoglobin >12%, uncontrolled hypertension, symptomatic chronic heart failure with reduced ejection fraction.

Interventions

Oral finerenone, 10 or 20 mg/d (*n* = 6519), or placebo (*n* = 6507).

Funding

Bayer AG.

*See Glossary. Some information provided by authors.

Results: Finerenone vs. placebo added to usual care in patients with type 2 diabetes and CKD

Outcome	Event rates		At a median 3 y	
	Finerenone	Placebo	RRR (95% CI)	NNT (CI)
Composite CV outcomes†	12.7%	14.4%	13% (5 to 21)‡	46 (29 to 109)
Composite kidney outcomes§	5.5%	7.1%	22% (12 to 32)‡	60 (38 to 142)
Any adverse event‖	86.1%	86.4%	0.4% (−1 to 2)	NS
			RRI (CI)	NNH (CI)
Hyperkalemia‖	12.0%	5.9%	104% (81 to 129)	17 (15 to 20)
Serious hyperkalemia‖**	1.1%	0.2%	330% (151 to 635	123 (90 to 182)

CV = cardiovascular; NS = not significant; other abbreviations defined in Glossary. Primary outcomes indicated by boldface.

†First event including CV death (RRR 12%, CI -2 to 23), non-fatal myocardial infarction (RRR 9%, CI −12 to 26), non-fatal stroke (RRR 1%, CI −21 to 18), or hospitalization for heart failure (RRR 22%, CI 8 to 33; NNT 33, CI 21 to 89). RRR, NNT, and CI calculated from control event rates and adjusted hazard ratios in article.

‡RRR and CI calculated from event rates alone and adjusted hazard ratios in article. The hazard ratio was adjusted for study, region, eGFR at screening, albuminuria, and history of CV disease.

§First event including kidney failure (RRR 16%, CI 1 to 29; NNT 45, CI 25 to 711), sustained ≥57% decrease in eGFR from baseline over ≥4 weeks (RRR 29%, CI 17 to 39; NNT 24, CI 18 to 42), or renal death (RRR 47%, CI −191 to 90). RRR, NNT, and CI calculated from control event rates and adjusted hazard ratios in article.

‖RRR, RRI, NNH, and CI calculated from event rates in article.

**Serious event resulting in death; was life-threatening; required hospitalization; caused persistent or significant disability/incapacity; was a congenital abnormality or birth defect; or judged by investigator to be serious or an important medical event.

Bottom line: In patients with type 2 diabetes and CKD, addition of finerenone to usual care reduced a composite of CV and kidney outcomes vs. placebo.

Commentary

Two large RCTs showed finerenone was effective for CV and kidney outcomes in patients with type 2 diabetes and albuminuric CKD. Pre-specified pooling of the RCTs by Agarwal and colleagues allows these effects to be explored with more precision. With finerenone, kidney failure or a doubling of serum creatinine was reported to be reduced by 23% and hospitalization for heart failure by 22%. These RRRs are similar to observed effects of sodium-glucose co-transporter-2 inhibitors (SGLT2i) in placebo-controlled trials (1).

FIDELITY reported that the relative benefits of finerenone on CV outcomes were similar across patient subgroups, but subgroups effects for kidney outcomes were not explored.

Except for hyperkalemia, finerenone appeared safe with no excess risk for serious acute kidney injury. Both RCTs selected participants with serum potassium ≤4.8 mmol/L at screening and implemented careful algorithmic monitoring. Whether based on laboratory data or investigator reports, risk for hyperkalemia with finerenone vs. placebo was approximately doubled. In FIDELIO-DKD, treatment withdrawal or interruption, respectively, were 2.3% and 11.0% in the finerenone group vs. 0.9% and 5.2% for the placebo group (2). In FIDELITY, permanent treatment withdrawal for hyperkalemia was 1.7% vs. 0.6% and serious hyperkalemia was relatively rare with a <1% excess risk for hospitalization for serious hyperkalemia observed over 3 years. In FIDELIO-DKD, other risk factors for hyperkalemia were higher baseline potassium and lower kidney function, while concomitant diuretics or an SGLT2i—which were prescribed in 57% and 5% of participants, respectively—were both associated with lower risk for hyperkalemia (2). This is consistent with findings from RCTs in heart failure which suggest SGLT2i vs. placebo reduce risk for severe hyperkalemia and discontinuation of mineralocorticoid receptor antagonists (1). Overall, provided that additional blood testing and the risk for serious hyperkalemia is acceptable, finerenone offers an important new treatment for patients with type 2 diabetes and albuminuric CKD; combining it with an SGLT2i may reduce risk of finerenone-associated hyperkalemia. Whether net benefits extend to patients with non-diabetic forms of CKD and heart failure with preserved ejection fraction are being assessed in ongoing trials.

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Disclosures: WGH is a finerenone trial data safety monitoring board member (remuneration declined). KM has disclosed no conflicts. The form can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=ANN-NNNN

References

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2. **Agarwal R, Joseph A, Anker SD, et al.** Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. J Am Soc Nephrol. 2022;33:225-237. 34732509