Title:	Bringing FIDELITY to the estimate of treatment effects of finerenone in chronic kidney disease due to type 2 diabetes

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Diabetes remains one of the most common causes of end stage kidney disease in the world. As such preventing the progression of diabetes related kidney disease is an important therapeutic target. At the same time many patients will also have concomitant cardiovascular disease or die of cardiovascular causes, therefore, prevention of cardiovascular events is an equally important goal of therapy in this group. In this issue of the journal Agarwal *et al*. present the results of The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis (FIDELITY) [1]. In this pooled, meta-analysis of two trials of patients with type 2 diabetes and mild to severe chronic kidney disease the authors report on the effect of the novel non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone, on the prevention of deterioration of kidney disease and adverse cardiovascular outcomes. The FIDELITY analysis consists of two trials, FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) [2] and FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD) [3]. The FIDELIO-DKD trial enrolled patients with chronic kidney disease secondary to type 2 diabetes with severely increased albuminuria and stage 3-4 CKD [2]. As this patient group are at high risk of kidney failure, the trial was powered to detect a reduction in kidney failure events. The FIGARO-DKD population consisted of patients with type 2 diabetes with stage 2–4 CKD and moderately increased albuminuria, or stage 1–2 CKD with severely increased albuminuria [3]. Therefore, they overlapped with FIDELIO-DKD and with their lower risk of kidney failure, the effect of finerenone on cardiovascular events was tested in this cohort. Both trials met

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their primary endpoint but are now combined in this pre-specified analysis of both trials. At first sight it may seem unnecessary to combine the trials given that they both met their primary outcome and there was some overlap in the populations studied. Indeed, the results of FIDELITY confirm the results of FIGARO-DKD and FIDELIO-DKD but the analysis adds important new information to the separate analyses (Graphical Abstract). It is important to remember that kidney failure was the primary endpoint of the FIDELIO-DKD and a cardiovascular composite the secondary outcome. The primary and secondary outcomes were the opposite in FIGARO-DKD. Without sophisticated hierarchical or prespecified planning of multiple outcomes, any trial is only powered to examine the primary outcome for which it was designed. Therefore, the results of FIGARO-DKD do not provide definitive information the effect of finerenone on kidney failure outcomes in those with less severe CKD and FIDELIO-DKD does not provide definitive information on the effect of finerenone on cardiovascular outcomes in those with more severe CKD [Graphical Abstract Figure]. FIDELITY bridges this gap now by confirming that across the spectrum of CKD studied in these trials, finerenone reduce the risk of the CV composite outcome and kidney composite outcome with no evidence of heterogeneity between the trials. While this is of importance to trialists and guideline writers, the pooled analysis of these two trials fills another, more clinically important, role. The results of the FIDELITY analysis allow clinicians to see the effect of finerenone across a broad spectrum of patients that they encounter in real life. Categorising physiological measures such as GFR and albuminuria simplifies the design of clinical trials, but it neglects the complexities of patients where risk is not so easily categorised (Figure) [4]. Risk is blurry and not easily compartmentalised, being determined

by more than just two physiological factors. However, clinical trials do not yet incorporate

sophisticated multi-variable risk when determining inclusion into a trial, and therefore we

continue to classify patients according to categories of continuous variables. FIDELITY

provides information on a broader range of patients analysed in a consistent manner than

either FIDELIO-DKD or FIGARO-DKD alone did. Furthermore, arbitrary cut offs can be even

more problematic in situations where there is a potential to misclassify patients. Measures

are often only obtained once at a screening visit and may ignore physiological as well as

measurement variation. Measures at the edges of categories can include or exclude patients

from trials that would otherwise benefit from the therapy under study and may

subsequently be excluded from receiving effective treatments based on arbitrary cut offs

first chosen by trialists, and later exacerbated by guidelines and payors. It could be argued

that FIDELIO-DKD and FIGARO-DKD on their own do show benefit on kidney progression and

cardiovascular outcomes but FIDELITY provides as more precise estimate of the effect and in

a broader range of patients than either trial alone, as well as much more safety data. Could

these issues not be solved by combing the populations at the outset and having co-primary

endpoints? This would be a much more complex endeavour with sample size calculations

being very difficult to calculate because of the broad underlying risk of the population and

difficulty in predicting event rates. Thus, meta-analysis becomes a powerful tool to describe

the effect of treatment across a broad range of patient groups establishing the kidney and

cardiovascular benefits of finerenone in patients with type 2 diabetes. Finerenone now joins

ACE inhibitors, sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1

receptor agonists as a drug to reduce the risk of cardiovascular and kidney outcomes in

patients with type 2 diabetes and kidney disease. There is one final important finding for the cardiologist from FIDELITY, it offers insight into which patients may benefit from finerenone in the future. In an analysis of the components of the cardiovascular outcomes the biggest relative risk reduction (22%) was in hospitalisations for heart failure. Heart failure has suffered from similar issues of artificial cut offs for ejection fraction which have only recently begun to be disentangled by guidelines [5]. While MRAs hold a class 1A recommendation for the treatment of heart failure with reduced ejection fraction trials of MRA in heart failure with preserved ejection fraction have not been so conclusive [5]. Finerenone is being tested in the FINEARTS-HF trial (NCT04435626) in a population with heart failure with preserved ejection fraction (≥40%) to determine if this non-steroidal MRA can improve outcomes in the spectrum of ejection fraction not covered by current guideline recommendations for MRAs. We will continue to define diseases, and risk, by cut offs in a measure of renal or cardiac function until trial design advances to accommodate the blurry nature of these definitions. Until then FIDELITY serves as yet another reminder that combining populations will continue to yield important insights into the efficacy of treatments in wider populations.
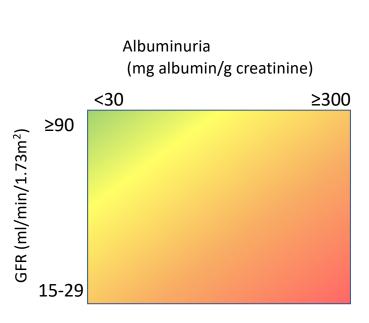
Conflicts of Interest

References

1. Insert reference to article this editorial is about

2. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G; FIDELIO-DKD Investigators. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020 Dec 3;383(23):2219-2229

3. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, Joseph A, Kolkhof P, Nowack C, Schloemer P, Ruilope LM; FIGARO-DKD Investigators. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021 Aug 28. doi: 10.1056/NEJMoa2110956. Epub ahead of print.

4. Levey AS , Eckardt KU , Dorman NM , Christiansen SL , Hoorn EJ , Ingelfinger JR , Inker LA , Levin A , Mehrotra R , Palevsky PM , Perazella MA , Tong A , Allison SJ , Bockenhauer D , Briggs JP , Bromberg JS , Davenport A , Feldman HI , Fouque D , Gansevoort RT , Gill JS , Greene EL , Hemmelgarn BR , Kretzler M , Lambie M , Lane PH , Laycock J , Leventhal SE , Mittelman M , Morrissey P , Ostermann M , Rees L ,

Ronco P , Schaefer F , St Clair Russell J , Vinck C , Walsh SB , Weiner DE , Cheung M , Jadoul M , Winkelmayer WC. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference. Kidney Int 2020;97:1117–1129.

5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726.

Figure

Risk according to categories of estimated glomerular filtration and albuminuria as categories used in guidelines and trials versus a representation of the gradient in risk found in patients

Risk defined in guidelines and trials

KDIGO risk			
Low risk			
Moderate risk			
High risk			
Very high risk			

				Albuminuria categories and range (mg albumin/g creatinine)		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30	30 to <300	≥300
eGFR stages and range (mL/min/1.73 m²)	G1	High and optimal	≥ 90			
	G2	Mild	60-89			
	G3a	Mild-moderate	45-59			
	G3b	Moderate-severe	30-44			
	G4	Severe	15-29			

Risk in patients

Albuminuria
(mg albumin/g creatinine)

GFR (ml/min/1.73m²)