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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
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.

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Conflicts of Interest
PSJ – Dr Jhund’s employer has been paid by Novartis, Astrazeneca, NovoNordisk and Bayer for work on clinical trials. Consulting, advisory board and speakers fees from Novartis, Astrazeneca and Boehringer Ingelheim and grants from Boehringer Ingelheim and Analog Devices Inc.

References

1. Insert reference to article this editorial is about


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

<table>
<thead>
<tr>
<th>KDIGO risk</th>
<th>Albuminuria categories and range (mg albumin/g creatinine)</th>
<th>Risk in patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>A1 Normal to mildly increased</td>
<td>Albuminuria (mg albumin/g creatinine)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>A2 Moderately increased</td>
<td>&lt;30</td>
</tr>
<tr>
<td>High risk</td>
<td>A3 Severely increased</td>
<td>30 to &lt;300</td>
</tr>
<tr>
<td>Very high risk</td>
<td></td>
<td>≥300</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR stages and range (mL/min/1.73 m²)</th>
<th>G1 High and optimal ≥ 90</th>
<th>G2 Mild 60-89</th>
<th>G3a Mild-moderate 45-59</th>
<th>G3b Moderate-severe 30-44</th>
<th>G4 Severe 15-29</th>
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