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RESEARCH LETTER

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Effect of finerenone on the occurrence of vision-threatening complications in patients with non-proliferative diabetic retinopathy: Pooled analysis of two studies using routine ophthalmological examinations from clinical trial participants (ReFineDR/DeFineDR)

Peter Rossing MD[1,2] | Justus G. Garweg MD[3,4] | Stefan D. Anker MD[5,6] | Takeshi Osonoi PhD[7] | Bertram Pitt MD[8] | Sylvia E. Rosas MD[9] | Luis Miguel Ruilope MD[10] | Dalong Zhu MD[11] | Meike Brinker MD[12] | David Finis MD[12] | Sergio Leal MD[13] | Thomas Schmelter PhD[14] | George Bakris MD[15]

[1]Steno Diabetes Center Copenhagen, Herlev, Denmark

[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]Swiss Eye Institute, Rotkreuz, and Berner Augenklinik, Bern, Switzerland

[4]Department of Ophthalmology, Inselspital, University of Bern, Bern, Switzerland

[5]Department of Cardiology (CVK), and Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany

[6]Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland

[7]Nakakinen Clinic, Naka, Japan

[8]University of Michigan School of Medicine, Ann Arbor, Michigan

[9]Joslin Diabetes Center and Harvard Medical School, Boston, Massachusetts

[10]Hypertension Unit and Cardiorenal Translational Laboratory, Madrid, Spain

[11]Department of Endocrinology and Metabolism, DrumTower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China

[12]Bayer AG, Wuppertal, Germany

[13]Bayer Consumer Care AG, Basel, Switzerland

[14]Bayer AG, Berlin, Germany

[15]American Heart Association Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, Illinois

Correspondence

Peter Rossing, MD, Steno Diabetes Center Copenhagen, Herlev, Denmark.
Email: peter.rossing@regionh.dk

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Peter Rossing and Justus G. Garweg contributed equally to this study.

1 | BACKGROUND/CONTEXT

Diabetic retinopathy (DR) and chronic kidney disease (CKD) are two major forms of microvascular complications in patients with type 1 diabetes and type 2 diabetes (T2D), with shared risk factors (such as poor glycaemic control, smoking, hypertension and dyslipidaemia) and clinical manifestations (microvascular lesions).[1] The steroid hormone aldosterone, which binds to mineralocorticoid receptors, promotes vascular pathology in the retina relevant to the development of DR[2]; antagonism of the retinal mineralocorticoid receptor–aldosterone system may delay progression.[3]

Finerenone, a potent and selective, orally administered, non-steroidal mineralocorticoid receptor antagonist (MRA), slowed progression of CKD and reduced the risk of cardiovascular outcomes versus placebo in patients with CKD and T2D in the FIDELIO-DKD (NCT02540993; n = 5674) and FIGARO-DKD (NCT02545049; n = 7352) randomized phase 3 trials.[4,5] In total, 2657 (46.8%) patients in FIDELIO-DKD and 2265 (30.8%) in FIGARO-DKD had DR at baseline.[6,7] No further details on DR were collected in these studies. However, data from participants who had routine ophthalmological assessments during the study periods were utilized in ReFineDR (NCT04477707) and DeFineDR (NCT04795726), two identical hypothesis-generating studies, to explore the effect of finerenone on progression of DR. Here, we report a pooled analysis of both studies combined.

2 | METHODS

2.1 | Study design

The studies were approved by the relevant independent ethics committees and health authorities and were conducted in accordance with the principles of the Declaration of Helsinki, as revised in 2008. Details of the independent ethics committees can be found in the FIDELIO-DKD and FIGARO-DKD protocols.[4,5]

Ophthalmological data from routine examinations were collected retrospectively from patients with a medical history of DR who participated in FIDELIO-DKD or FIGARO-DKD at selected centres (see the supporting information). To minimize bias, participant inclusion was masked to treatment assignment in FIDELIO-DKD/FIGARO-DKD. Patient demographic data were derived from the existing FIDELIO-DKD/FIGARO-DKD database.

In both studies, patients aged 18 years or older with T2D and CKD, as defined by international guidelines, treated with optimized renin–angiotensin system (RAS) blockade therapy, were included. Eligible patients had a routine ophthalmological examination between 6 months prior and 1 month post-randomization showing treatment-naïve non-proliferative DR (NPDR) in at least one eye, and at least one subsequent routine ophthalmological examination (see the supporting information). Standard grading for NPDR was used as per international guidelines.[8] Exclusion criteria were diabetic macular oedema (DME), proliferative DR (PDR) or anterior segment complications; any other retinal disease that could interfere with study objectives (e.g. neovascular age-related macular degeneration or retinal vein occlusion); and prior/planned ocular interventions (retinal laser treatment, intravitreal injection or vitrectomy). All patients provided signed informed consent to participate in ReFineDR/DeFineDR.

2.2 | Outcomes

The primary endpoint was progression of NPDR as defined by the occurrence of vision-threatening complications (VTCs), a composite endpoint comprising development of anterior segment neovascularization, DME or progression to PDR, in at least one eye up to 2 years after treatment initiation (day of randomization in FIDELIO-DKD/FIGARO-DKD). Time to event analyses, including time to VTC after 2 years, and time to required ocular interventions (laser treatment, intravitreal injection or vitrectomy) in at least one eye at any time, were assessed post hoc. Time to VTC was also assessed in subgroups of patients with an HbA1c of 58 mmol/mol or less (≤ 7.5%) and of more than 58 mmol/mol (> 7.5%).

2.3 | Statistical analyses

The primary endpoint was assessed using a two-sided *z*-test for the difference of two proportions (unpooled variances) using normal approximation. Cumulative incidence probabilities with 95% CIs for the time-to-event endpoints were computed using Kaplan–Meier estimates.

3 | RESULTS

Of 376 potentially eligible patients, 132 did not meet the eligibility criteria; therefore, 244 were included in ReFineDR/DeFineDR. Of these 244 patients, 134 had received at least one dose of finerenone and 110 had received placebo. In total, 216 patients (finerenone: n = 123, placebo: n = 93) completed the treatment course in FIDELIO-DKD and FIGARO-DKD.

At baseline, 68.7% (92/134) and 71.8% (79/110) of patients in the finerenone and placebo groups had mild/moderate NPDR, and 3.0% (4/134) and 10.0% (11/110) had severe NPDR, respectively (Table S1). Fewer patients in the finerenone group had a urinary albumin-creatinine ratio of 33.9 mg/mmol or higher (≥ 300 mg/g) (56.0% [75/134] vs. 68.2% [75/110]) and diabetes duration of 20 years or longer (24.6% [33/134] vs. 38.2% [42/110]). Mean baseline HbA1c was similar between the two groups (finerenone: 66.7 mmol/mol [8.25%]; placebo: 65.9 mmol/mol [8.18%]).

By 2 years, 3.7% (5/134) and 6.4% (7/110) of patients in the finerenone and placebo groups had experienced a VTC in at least one eye (difference −0.026 [95% CI −0.082, 0.029]) (Figure 1). The number of VTCs increased beyond 2 years, with Kaplan–Meier-estimated

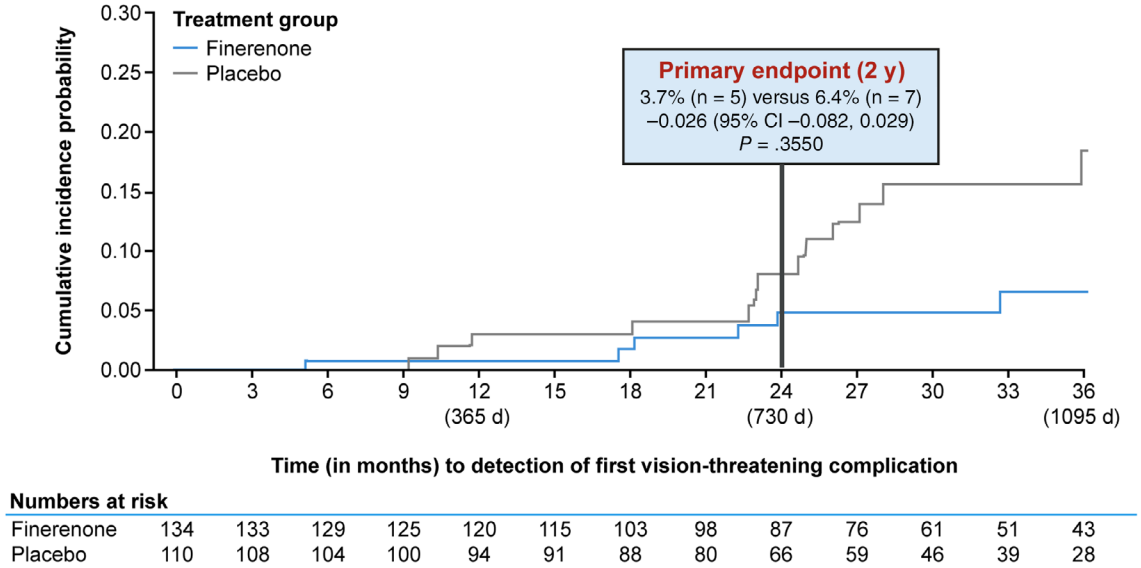

FIGURE 1 Time to vision-threatening complication (Kaplan–Meier analysis)

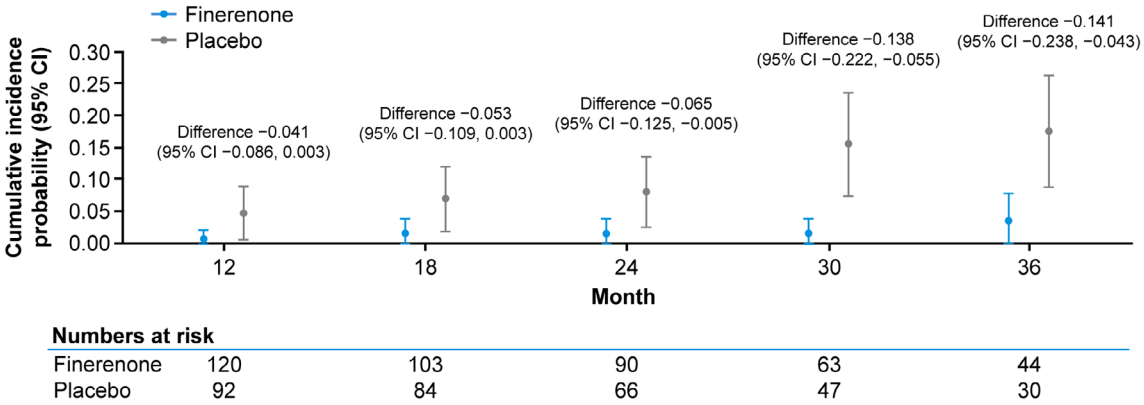

FIGURE 2 Cumulative incidence probability of a required ocular intervention

cumulative incidence probabilities favouring finerenone increased at 30 months (difference −0.109 [95% CI −0.202, −0.016]) and 36 months (difference −0.118 [95% CI −0.229, −0.007]). The numerical benefits of finerenone were consistent for time to DME or progression to PDR, and in the subgroups of patients with a baseline HbA1c of 58 mmol/mol or less (≤ 7.5%) and of more than 58 mmol/mol (> 7.5%) (Table S2), although 95% CIs for the differences at most timepoints included zero. In addition, the numerical benefits of finerenone versus placebo for time to VTC and time to required ocular intervention were generally consistent by baseline severity of NDPR and duration of T2D (Tables S3 and S4), although some 95% CIs for the differences included zero.

Fewer patients in the finerenone group versus the placebo group had required ocular interventions (four [3.0%] vs. 17 [15.5%]), with cumulative incidence probabilities favouring finerenone at 24, 30 and 36 months (Figure 2).

4 | CONCLUSIONS

This was a hypothesis-generating analysis suggesting a potential benefit of finerenone in the delay of progression of NPDR, independent of baseline HbA1c. Potential benefits of finerenone were also observed in the prevention of required ocular interventions.

While the analysis provides a higher level of evidence compared with standard cohort studies, the set-up resulted in some limitations; because of a lack of randomization and stratification, an imbalance in some baseline characteristics was observed. In particular, the higher proportion of patients with severe NPDR at baseline in the placebo group compared with the finerenone group may have led to more frequent follow-up in this group, impacting time-to-event analyses. In addition, lower-than-expected recruitment and a lack of data availability impacted data collection. Consequently, the overall number of VTCs was small, limiting power to detect between-group differences.

Additionally, most participants were at an early stage of disease at baseline and were on optimized RAS therapy, which may also have limited event rates. Longer term observation may be required to detect significant differences in disease progression in this population. Furthermore, as eye examinations were not predefined as an outcome measure, the studies relied on routine ophthalmological examinations, which may have affected data quality and certainly affected quantity.

Current ocular treatments for DR, such as laser photocoagulation, intravitreal injection of antivascular endothelial growth factor agents or corticosteroids and vitreoretinal surgery, are invasive to the eye and generally only applicable upon progression of disease. Management of NPDR is typically limited to control of blood glucose, or other related factors such as blood pressure and dyslipidaemia. To date, the only oral therapies for which a potential effect on progression or incidence of DR has been shown are RAS blockers, including enalapril, losartan and candesartan.[9,10] Although steroidal MRAs were effective in delaying central serous chorioretinopathy in small clinical studies,[11] and antagonized the mineralocorticoid receptor in preclinical studies,[3] this is the first analysis to assess a nonsteroidal MRA for delaying the progression of NPDR. Notably, the potential benefits of finerenone versus placebo observed in the current studies were in addition to optimized RAS therapy, which was received by all enrolled patients.

In conclusion, the potential benefit of finerenone observed in this analysis was consistent across outcomes. As this analysis was exploratory and hypothesis-generating in nature, definitive conclusions cannot be drawn. However, these findings suggest that randomized studies with adequate power to detect a potential benefit of finerenone in delaying NPDR progression should be considered, particularly given the lack of alternative options for oral treatment of DR.

AUTHOR CONTRIBUTIONS

PR, JGG, SDA, TO, BP, SER, LMR, DZ, MB, DF, SL, TS and GB are responsible for the work described in this article. All authors were involved in at least one of the following: study conception; design of work; or acquisition, analysis and interpretation of data. All authors revised the article critically for important intellectual content and provided final approval of the published version. MB and SL accept full responsibility for the work and/or the conduct of the study and had access to the data.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point and process of data access. As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

ORCID

Peter Rossing https://orcid.org/0000-0002-1531-4294
Dalong Zhu https://orcid.org/0000-0002-1064-1261

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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