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Running title: Finerenone in Chinese T2DM and CKD

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Abstract

Background: This prespecified subgroup analysis of the FIDELIO-DKD trial aimed to evaluate the efficacy and safety of finerenone in patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM) in China.

Methods: Three hundred and seventy-two participants were recruited from 67 centers in China and randomized 1:1 to oral finerenone or placebo with standard therapy for T2DM. The primary composite outcome included kidney failure, sustained decrease of estimated glomerular filtration rate (eGFR) ≥ 40% from baseline over at least 4 weeks, or renal death. The key secondary composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

Results: After a median follow-up of 30 months, the finerenone group showed a relative risk reduction (RRR) of 41% (hazard ratio [HR]=0.59, 95% confidence interval [CI], 0.39 to 0.88; *p*=0.009) for the primary composite outcome compared with placebo, consistent across its components with treatment benefits with finerenone. Based on an absolute between-group difference of 12.2% after 30 months, the number of patients who needed to be treated (NNT) with finerenone to prevent one primary outcome event was eight (95%CI: 4 to 84). For the key secondary composite outcome, the finerenone group showed a RRR of 25% (HR=0.75, 95% CI, 0.38 to 1.48; *p*=0.408). Adverse events were similar between the two groups. The effects of finerenone on blood pressure were modest. No gynecomastia events were reported in the study. Hyperkalemia leading to discontinuation occurred in eight (4.3%) and two (1.1%) participants in the finerenone and control groups, respectively. The incidence of acute kidney injury was comparable between the two groups (1.6% vs. 1.6%).

Conclusions: Finerenone resulted in lower risks of CKD progression than placebo and a balanced safety profile in Chinese patients with CKD and T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is the leading cause of chronic kidney disease (CKD) worldwide [1], with a prevalence of CKD caused by T2DM of around 130 million in 2019 and nearly 400,000 deaths and, as a result, imposing heavy medical and economic burden worldwide [2]. About 20%-40% of patients with T2DM have CKD [3-5]. In China, the economic growth of the last decades increased sedentary behaviors and carbohydrate and saturated fat consumption, leading to rising rates of T2DM [6]. According to estimates, the prevalence of diabetes in China was 10.9% in 2013 and 12.4% in 2018, affecting more than 150 million people [7, 8]. Therefore, CKD consequent to diabetes evolved in the past 10 years in China. The proportion of patients with CKD due to DM (DM-CKD) has exceeded that of CKD due to glomerulonephritis (GN-CKD) since 2011 [9]. The prevalence of diabetic nephropathy among patients with T2DM in China is about 21.8% [10]. A similar rise in T2DM-associated CKD has also been observed in other Asian regions [11].

Finerenone is a non-steroidal selective mineralocorticoid receptor antagonist (MRA) that blocks sodium reabsorption and the overactivation of mineralocorticoid receptors (MR). By exerting powerful anti-inflammatory and antifibrotic effects, finerenone protects the kidney and cardiovascular system [12-15]. FIDELIO-DKD, a multicenter, global phase III randomized controlled trial (NCT02540993) involving 5734 participants, showed that finerenone reduced the risk of CKD progression and cardiovascular events compared with placebo in patients with T2DM and CKD [16]. In light of these findings, finerenone was approved by the FDA for treating patients with CKD and T2DM, and in China, it has also been approved by the National Medical Products Administration (NMPA) [17].

Some characteristics are different in Asian and Chinese patients with T2D and CKD compared with other regions, including a high prevalence of a raised urinary albumin/creatinine ratio (UACR) [18], high risk of end-stage renal disease (ESRD) [19], and high dietary sodium intake [20]. To investigate the effects of finerenone in patients of various races and regions, it would be useful to analyze the activity of finerenone in the Chinese patients of the FIDELIO study.

The present study is a prespecified subgroup analysis of the Chinese participants' data from the FIDELIO-DKD study, which aimed to evaluate the efficacy and safety of finerenone in Chinese patients.

Methods

Participants and study design

The FIDELIO-DKD study (NCT02540993) was a multicenter, randomized, double-blind, placebo-controlled phase III trial involving 5734 participants. FIDELIO-DKD took place in 48 countries, including 67 centers in China (Supplementary Table 1). The present study was a prespecified subgroup analysis and analyzed all Chinese participants (n=372) who participated in the FIDELIO-DKD trial.

The study design and main results of FIDELIO-DKD have been published recently [16, 21]. The participants in FIDELIO-DKD were 18 or older, with T2DM and CKD (defined as a UACR of 30 to <300 mg/g, an estimated glomerular filtration rate [eGFR] of 25 to < 60 ml/min/1.73 m^2, and a history of diabetic retinopathy; or a UACR of 300 to 5000 mg/g and an eGFR of 25 to < 75 ml/min/1.73 m^2), and were uptitrated for at least 4 weeks to the maximally tolerated labeled dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) before the run-in period and had serum potassium of $\leq$ 4.8 mmol/L at the screening visit, but could have higher values at baseline visit. The detailed inclusion and exclusion criteria are provided in the previous publication [16]. FIDELIO-DKD followed the Declaration of Helsinki, was approved by the local ethics committees of each participating center, and all participants provided written informed consent.

Procedure

Eligible patients were randomly assigned to receive oral finerenone or placebo in a 1:1 ratio. A dose of 10 mg once daily was prescribed to participants with an eGFR of < 60 ml/min/1.73 m^2 at screening, and a dose of 20 mg once daily was prescribed for participants with an eGFR of ≥ 60 ml/min/1.73 m^2 at screening. In the case of a serum potassium level < 4.8 mmol/L and a stable eGFR, an increase in dose from 10 mg once daily to 20 mg once daily was recommended after 1 month of treatment. The dose of finerenone could be decreased from 20 to 10 mg once daily at any time after the initiation of treatment. If serum potassium concentrations exceeded 5.5 mmol/L, finerenone or placebo was withheld; treatment was resumed with 10 mg at 5.0 mmol/L or lower. The previous publication provides the detailed information about dosing regimens [16]. Once randomization was complete, the follow-up visits were conducted on month 1, month 4, and every 4 months thereafter.

Outcomes

The primary composite kidney outcome included kidney failure, a sustained drop in eGFR of at least 40% from baseline over at least 4 weeks, or death from renal causes, based on time-to-event analysis. Kidney failure was defined as eGFR < 15 ml/min/1.73 m^2 or ESRD. Patients who received long-term dialysis (≥ 90 days) or underwent kidney transplantation were considered to have ESRD. Following the initial measurement, an additional central laboratory serial measurement was required at least four weeks later to confirm the eGFR outcome. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [22].

The key secondary cardiovascular outcome was the composite of time to death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The secondary composite kidney outcome included kidney failure, a sustained drop in eGFR of ≥ 57% from baseline over ≥ 4 weeks, or death from renal causes. Death from any cause, hospitalization for any cause, and change in UACR from baseline to month four were also evaluated. A clinical event committee without access to enrollment information reviewed all reported outcomes.

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were considered safety outcomes. TEAE refers to an AE that developed or worsened within 3 days from the initial to the last dose.

Statistical analysis

SAS 9.4 software (SAS Institute) was used to perform all statistical analyses. The efficacy analyses were conducted on the full analysis set (FAS), which included all participants after randomization, while the safety analyses were conducted on the safety analysis set. The continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate. Categorical variables were presented as numbers and percentages. Kaplan-Meier (KM) methods and Cox proportional hazard models were used to analyze time-to-event variables. A forest plot was created for all the time-to-event variables, and the number of events per 100 patient-year, hazard ratio (HR), 95% confidence interval (CI), and p-value were calculated. A two-sided $p<0.05$ was considered statistically significant.

Results

Participants

A total of 372 participants from China were enrolled in the FIDELIO-DKD study, with 188 (50.5%) in the finerenone group and 184 (49.5%) in the placebo group. The mean age of the participants was 60.3 ± 10.1 years old, and the mean duration of diabetes was 13.7 ± 7.9 years. The median UACR was 1270 (IQR: 605, 2198) mg/g, and the mean eGFR was 45.6 ± 11.3 ml/min/1.73 m^2. The baseline characteristics of the participants are shown in Table 1. The baseline characteristics and concomitant medications were balanced between the finerenone and placebo groups.

The median follow-up of all participants was 30 months. A total of 89.2% of participants achieved treatment compliance of 80%-120%, with 88.3% in the finerenone group and 90.2% in the placebo group, and the mean daily dose was 15.4 and 16.5 mg in the respective groups.

Efficacy outcomes

The incidence of the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes was significantly lower in the finerenone group than in the placebo group, occurring in 40 patients (21.4%) and 61 patients (33.2%), respectively (hazard ratio [HR]=0.59, 95% confidence interval [CI], 0.39 to 0.88; p=0.009). On the basis of an absolute between-group difference of 12.2% after 30 months, the number of patients who needed to be treated (NNT) with finerenone to prevent one primary outcome event was eight (95%CI: 4 to 84). The difference was consistent across outcome components of the primary endpoint, showing a treatment benefit in the finerenone group (Fig. 1 and 2). The main component driving the result of the primary composite kidney outcome was that finerenone lowered the risk of the participants with a sustained drop in eGFR of at least 40% from baseline over at least 4 weeks compared to placebo (HR=0.59, 95% CI: 0.39 to 0.89; p=0.011), with incidences of 9.99 (95% CI: 7.07 to 13.4) and 16.21 (95% CI: 12.3 to 20.6) participants with an event per 100 patient-years, respectively (Fig. 2).

For the key secondary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), 15 events (8.0%) occurred in the finerenone group, and 19 events (10.3%) occurred in the placebo group (HR=0.75, 95% CI, 0.38 to 1.48; *p*=0.408) (Fig. 2).

There were no significant between-group differences in the risk of death from any cause and the incidence of hospitalization (Fig. 2). There was a trend of better secondary composite kidney outcome events (kidney failure, a sustained decrease of ≥ 57% in the eGFR from baseline, or death from renal causes) in the finerenone group (28 patients [14.9%] in the finerenone group and 39 patients [21.2%) in the placebo group, HR=0.68, 95%CI: 0.42-1.11, p=0.12) (Fig. 2). Compared with placebo, finerenone reduced UACR by 26.8% from baseline to month 4 (ratio of least-squares means 0.73; 95% CI: 0.66 to 0.82).

Safety

The safety profiles were comparable between the two groups. A total of 48.4% of the participants in the finerenone group and 54.3% in the placebo group experienced serious TEAE. Eleven (5.9%) in the finerenone group and six (3.3%) participants in the placebo group discontinued treatment due to TEAEs. One (0.5%) and two (1.1%) deaths were caused by treatment-related TEAEs that occurred in the finerenone and placebo groups, respectively (Table 2).

The hyperkalemia-related TEAEs were higher in the finerenone group compared with the placebo group (37.2% vs. 25.5%). A numerically greater change in serum potassium from baseline was observed in the finerenone group than in the control group at each visit (Fig. 3). The incidences of participants with serum potassium levels of > 5.5 mmol/L and > 6.0 mmol/L were 20.7% (39/188) and 3.7% (7/188) in the finerenone group, and 10.5% (19/181) and 2.2% (4/182) in the placebo group, respectively. Hyperkalemia leading to treatment discontinuation occurred in eight (4.3%) and two (1.1%) participants in the finerenone and placebo groups, respectively. Three (1.6%) patients in the finerenone group experienced hyperkalemia leading to hospitalization, and no hyperkalemia-related death was reported. The incidence of acute kidney injury was comparable between the two groups (1.6% vs. 1.6%) (Table 2).

Finerenone had modest effects on blood pressure. The mean systolic blood pressure changes from baseline to 1 and 12 months were -3.07 and -1.15 mmHg with finerenone, and 2.86 and 1.82 mmHg with placebo, respectively (Supplementary Table 1). No gynecomastia events or breast pain were reported in this subgroup analysis.

Discussion

This study was a subgroup analysis of the Chinese participants enrolled in the phase III FIDELIO-DKD trial. In line with the primary endpoint of the original trial, finerenone significantly reduced the risk of CKD progression in Chinese patients with CKD and T2DM [16]. In addition, the risk of cardiovascular events was numerically lower in the finerenone group than in the placebo group. These results suggested that in Chinese patients with CKD and T2DM, finerenone might be an effective renal and cardiovascular protective treatment option.

Compared with the global results, the participants in the Chinese subgroup were younger (60.3 ± 10.1 years old in this study vs. 65.6 ± 9.1 years old in the global study), with more males (78.0% in this study vs. 70.2% in the original study), and with a shorter duration of T2DM (13.7 ± 7.9 years in this study vs. 16.6 ± 8.8 years in the original study). The eGFR and systolic blood pressure were similar in the two studies. However, the participants in this subgroup showed higher UACR at baseline than in the overall study (1326.61 [IQR: 607.32-2148.56] in the finerenone group and 1210.41 [IQR: 601.73-2329.66] in the placebo group in this study, 833 [IQR: 441-1628] and 867 [IQR: 453-1645] in the original study, respectively). These findings suggested that although the Chinese participants included in this study were younger, with shorter diabetes duration and similar eGFR, their conditions might be more severe, as assessed by a higher baseline UACR. It was also demonstrated by the higher incidence of the primary composite endpoint in the placebo group in the Chinese subpopulation (33.2%) than in the whole study population (21.1%) [16].

In the Chinese sub-population, finerenone significantly reduced the risk of the primary composite kidney outcome by 41% compared with placebo, while in the overall population, the risk of the primary composite kidney outcome was reduced by 18% [16]. There might be several reasons for reducing the risk of primary outcomes in the Chinese population. First, the Chinese population has a high-salt diet that may cause a higher renal risk and benefit more from MRA. According to the INTERMAP study, the Chinese population consumes 13.3 g of salt daily, which is higher than that in other countries (8.5 g in the UK and 9.5 g in the USA) and more than twice what the World Health Organization recommended [23, 24]. Although awareness is on the rise and efforts have been made to reduce sodium consumption in the past years, sodium intake is still very high across all regions in China [25]. Evidence has shown the relationship between a high-salt diet and CKD progression through increased blood pressure, sympathetic activity, oxidative stress, inflammation, etc. [24, 26, 27, 28]. A high salt diet can produce MR activation through aldosterone-dependent and -independent pathways, leading to inflammation and fibrosis. Previous studies showed that high dietary salt blunts the antiproteinuric effect of ACEIs/ARBs therapy [24, 29]. In a post hoc analysis of the EVALUATE trial, the eplerenone-treated patients in the highest sodium excretion tertile exhibited significantly greater reduction in UACR than the placebo subjects in the same tertile, supporting the hypothesis that excessive salt intake can enhance resistance to RAS blockade by activating MR, when MRA may be effective for these patients [30]. In a preclinical study, Hirohama et al. found that finerenone improved glomerular injury in uninephrectomized db/db mice fed a high salt diet [31]. Second, although patients with known significant non-diabetic kidney disease were excluded from the FIDELIO-DKD study [16] due to limited biopsy diagnosis in clinical practice, there might be some T2DM patients with CKD caused by other underlying etiologies. The pathology spectrum of CKD in China is different compared with other countries. Although CKD caused by T2DM is rising in China, a large proportion of CKD is still caused by glomerulonephritis, idiopathic membranous nephropathy, IgA nephropathy, and lupus nephritis [32-35], among others, which might benefit more from anti-inflammation and anti-fibrosis effect of MRA. The ongoing phase III study FIND-CKD (NCT05047263) investigating the efficacy and safety of finerenone on non-T2DM-related CKD might provide evidence for the assumption.

The trend of the key secondary cardiovascular outcome in Chinese participants was consistent with that of the whole population in the original study. In the FIDELIO-DKD trial, finerenone significantly reduced the risk of key secondary cardiovascular outcomes (HR=0.86, 95%CI: 0.75 to 0.99, p=0.03) [16]. In the present study, although there were no statistically significant differences due to the small sample size of the subpopulation, finerenone showed a potential cardiac protection effect in Chinese patients.

Finerenone was well-tolerated by Chinese participants. Only eleven (5.9%) participants in the finerenone group and six (3.3%) in the placebo group discontinued treatment due to TEAE. The incidence of investigator-reported hyperkalemia-related AEs were higher in the finerenone (37.2% for China; 18.3% for global) and placebo (25.5% for China and 9.0% for global) groups [16, 36]. However, it seems to be an over-reporting, as the percentage of serum hyperkalemia > 5.5 mmol/L (20.7% for China and 21.4% for global) and >6.0 mmol/L 3.7% for China and 4.5% for global) in the central laboratory measurements in the finerenone and the placebo groups were similar in Chinese participants and global participants.

This study has some limitations. It was an analysis with a limited sample size. More further studies and real-world studies are needed to provide evidence.

Finerenone resulted in lower risks of CKD progression than placebo and a trend toward cardiovascular benefits, with a balanced safety profile and manageable risk of hyperkalemia in Chinese patients with CKD and T2DM.

Statements

Acknowledgments

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Statement of Ethics

The study was approved by the local ethics committees of each participating center, and all participants provided written informed consent.

Conflict of Interest Statement

Li Wang is an employee of Bayer. The other authors have no conflicts of interest to declare.

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Author Contributions

Zhihong Liu: contribution to study design, Chinese subject enrollment, data analysis and interpretation, manuscript writing and review. Haitao Zhang: contribution to the data analysis and interpretation of Chinese subgroup, manuscript writing and review. Li Wang: contribution to data analysis. The other authors (Jingyuan Xie, Chuanming Hao, Xuemei Li, Dalong Zhu, Hongguang Zheng, Xudong Xu, Zhaohui Mo, Weiping Lu, Yibing Lu, Chaoqing Wu, Nanwei Tong) have contributed to the data analysis and interpretation of Chinese subgroup, manuscript writing and review.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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Figure legends

Fig. 1. Primary and key secondary composite outcomes in Chinese patients. Outcomes were assessed in time-to-event analyses. (A) Primary kidney composite outcome (a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes in the finerenone and placebo groups). (B) Key secondary cardiovascular composite outcome (the composite of time to death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure).

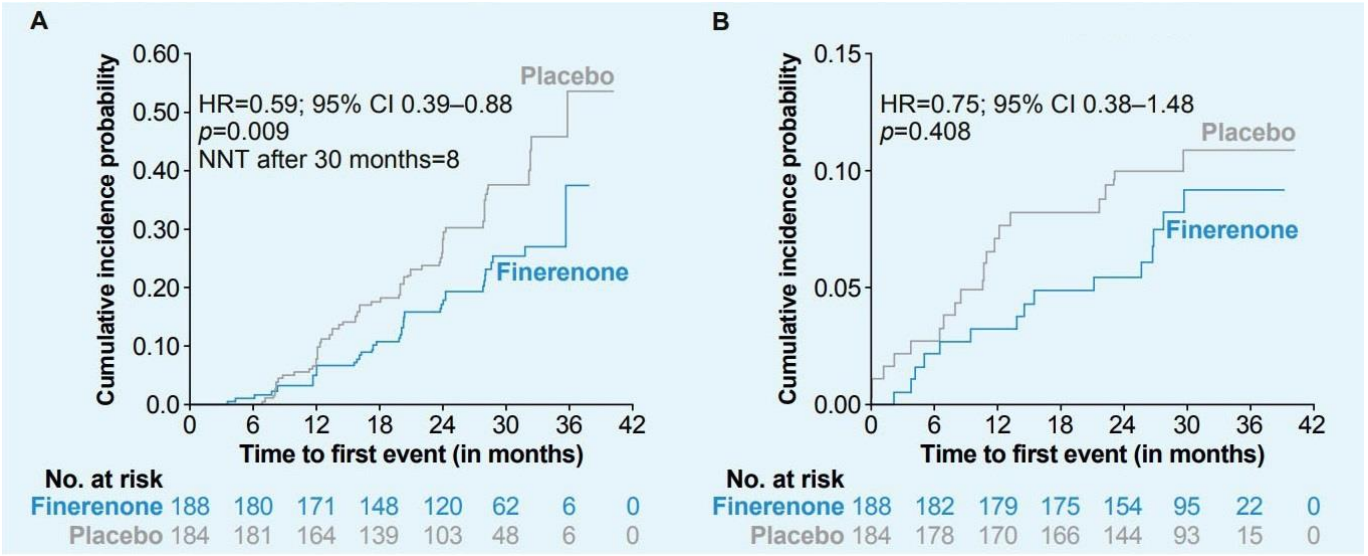
* Time to kidney failure (sustained ≥ 40% decrease in eGFR from baseline over ≥ 4 weeks, or renal death).

Time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

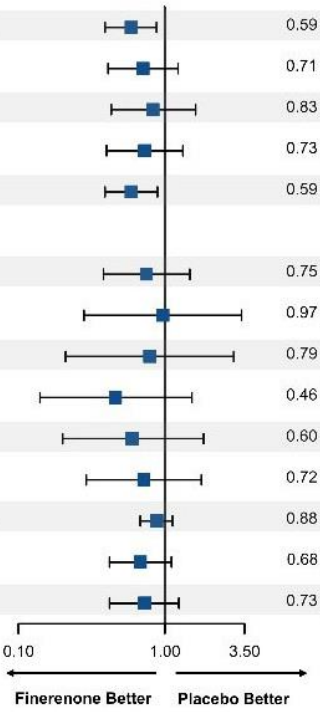
CV, cardiovascular; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.

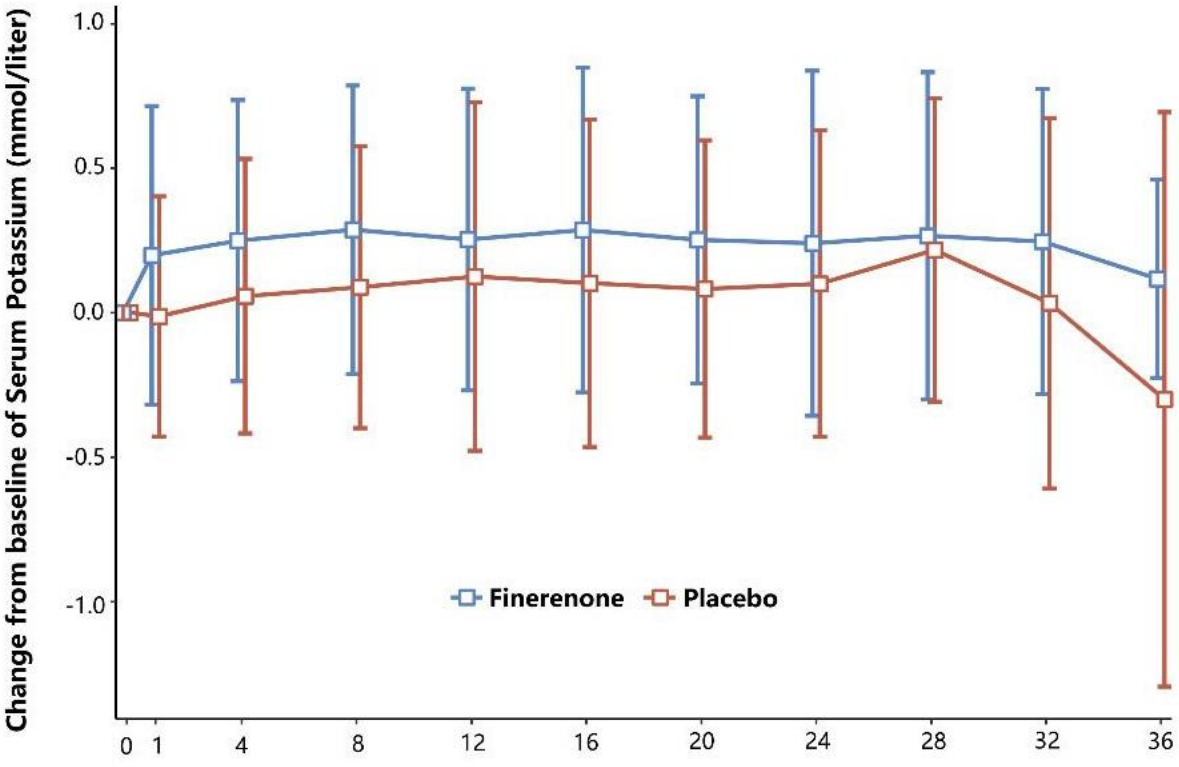
Fig. 2. Efficacy outcomes. The hierarchical prespecified efficacy outcomes in Chinese patients. Outcomes were assessed in time-to-event analyses. CI, confidence interval; eGFR, estimated glomerular filtration rate.

Fig. 3. Effects on serum potassium over time in Chinese patients. Effects of finerenone and placebo on serum potassium levels in the safety analysis set. Potassium was assessed by the central laboratory. Plus–minus values are means ± SD. The I bars indicate 95% confidence intervals.



Outcome	Finerenone (N=188)	Placebo (N=184)	Finerenone (N=188)	Placebo (N=184)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	40 (21.3)	61 (33.2)	10.51	17.03	0.59 (0.39–0.88)	0.009
Kidney failure	23 (12.2)	30 (16.3)	5.79	7.78	0.71 (0.41–1.23)	0.219
End-stage kidney disease	16 (8.5)	19 (10.3)	3.61	4.37	0.83 (0.43–1.62)	0.584
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	19 (10.1)	24 (13.0)	4.79	6.24	0.73 (0.40–1.33)	0.297
Sustained decrease of ≥40% in eGFR from baseline	38 (20.2)	58 (31.5)	9.99	16.21	0.59 (0.39–0.89)	0.011
Death from renal causes	0	1 (0.5)	—	—	—	—
Key secondary composite outcome	15 (8.0)	19 (10.3)	3.39	4.49	0.75 (0.38–1.48)	0.408
Death from cardiovascular causes	5 (2.7)	5 (2.7)	1.09	1.11	0.97 (0.28–3.34)	0.958
Nonfatal myocardial infarction	4 (2.1)	5 (2.7)	0.89	1.13	0.79 (0.21–2.96)	0.730
Nonfatal stroke	4 (2.1)	8 (4.3)	0.88	1.83	0.46 (0.14–1.53)	0.194
Hospitalization for heart failure	5 (2.7)	8 (4.3)	1.10	1.83	0.60 (0.20–1.84)	0.366
Death from any cause	8 (4.3)	11 (6.0)	1.75	2.45	0.72 (0.29–1.78)	0.469
Hospitalization for any cause	116 (61.7)	121 (65.8)	41.73	48.02	0.88 (0.68–1.13)	0.317
Secondary composite kidney outcome	28 (14.9)	39 (21.2)	7.16	10.25	0.68 (0.42–1.11)	0.120
Sustained decrease of ≥57% in eGFR from baseline	23 (12.2)	31 (16.8)	5.87	8.14	0.73 (0.42–1.25)	0.248





No. of Patients					
Finerenone	188	183	178	146	6
Placebo	184	181	174	135	6
Mean Change from Baseline (mmol/liter)					
Finerenone	Ref.	0.25	0.25	0.24	0.12
Placebo	Ref.	0.06	0.13	0.10	-0.30

Table 1. Demographic and characteristics of the Chinese patients at baseline.

Characteristic	Finerenone (n=188)	Placebo (n=184)
Age (years), mean ± SD	59.85 ± 10.16	60.68 ± 10.13
Male sex, n (%)	145 (77.1)	145 (78.8)
Duration of diabetes (years), mean ± SD	13.31 ± 7.43	14.17 ± 8.40
HbA1C (%), mean ± SD	7.47 ± 1.37	7.44 ± 1.33
Systolic blood pressure (mmHg), mean ± SD	135.83 ± 14.6	132.89 ± 15.88
eGFR (ml/min/1.73 m^2), mean ± SD	45.88 ± 11.37	45.25 ± 11.22
eGFR (ml/min/1.73 m^2), n (%)		
≥60 ml/min/1.73 m^2	21 (11.2)	19 (10.3)
45 to <60 ml/min/1.73 m^2	78 (41.5)	70 (38.0)
25 to <45 ml/min/1.73 m^2	88 (46.8)	92 (50.0)
<25 ml/min/1.73 m^2	1 (0.5)	3 (1.6)
UACR (mg/g), median (IQR)	1326.61 (607.32-2148.56)	1210.41 (601.73-2329.66)
UACR (mg/g), n (%)		
30 to <300	18 (9.6)	14 (7.6)
≥300	170 (90.4)	170 (92.4)
Serum potassium (mmol/L), mean ± SD	4.29 ± 0.44	4.28 ± 0.42
Baseline medications, n (%)		
ACE inhibitors	21 (11.2)	23 (12.5)
ARB	167 (88.8)	161 (87.5)
Diuretics	29 (15.4)	45 (24.5)
Statins	104 (55.3)	93 (50.5)
Potassium-lowering agent [#]	0	2 (1.1)
Glucose-lowering therapy	181 (96.3)	179 (97.3)
Insulin	147 (78.2)	141 (76.6)
GLP-1 receptor agonist	2 (1.1)	4 (2.2)
SGLT2 inhibitor	0	0
HDL (mg/dL), mean ± SD	48.42 ± 15.73	48.34 ± 16.03
LDL (mg/dL) [†], mean ± SD	93.60 ± 44.70	88.75 ± 36.93
Triglycerides, mean ± SD	210.89 ± 170.96	210.95 ± 147.89

[#] Including sodium polystyrene sulfonate, calcium polystyrene sulfonate, and potassium-binding agents;

† The sample size for finerenone group is 180; the sample size for placebo group is 175.

SD, standard deviation; HbA1C, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; GLP-1, glucagon-like peptide 1; SGLT2, sodium glucose cotransporter-2; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2. Safety outcomes in China subpopulation.

Event	Finerenone (N=188)	Placebo (N=184)
Any AE	181 (96.3%)	181 (98.4%)
Any AE leading to discontinuation of study drug	15 (8.0%)	11 (6.0%)
Any SAE	111 (59.0%)	113 (61.4%)
Any AE with outcome death	3 (1.6%)	7 (3.8%)
Any TEAE	176 (93.6%)	179 (97.3%)
Any treatment-related TEAE	70 (37.2%)	68 (37.0%)
Any TEAE leading to treatment discontinuation	11 (5.9%)	6 (3.3%)
Any Serious TEAE	91 (48.4%)	100 (54.3%)
Any treatment-related Serious TEAE	5 (2.7%)	10 (5.4%)
Any Serious TEAE leading to treatment discontinuation	2 (1.1%)	4 (2.2%)
Any serious TEAE leading to death	1 (0.5%)	2 (1.1%)
Any hyperkalemia related TEAE	70 (37.2%)	47 (25.5%)
Serious	4 (2.1%)	1 (0.5%)
Leading to hospitalization	3 (1.6%)	0 (0.0%)
Leading to treatment discontinuation	8 (4.3%)	2 (1.1%)
Any renal-related TEAE		
Leading to hospitalization	2 (1.1%)	2 (1.1%)
Leading to treatment discontinuation	1 (0.5%)	0
Glomerular filtration rate decreased	3 (1.6%)	2 (1.1%)
Acute kidney injury	3 (1.6%)	3 (1.6%)

AE, adverse event; TEAE, treatment-emergent adverse event; SAE; serious adverse event.