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Association of Finerenone Use With Reduction in Treatment-Emergent Pneumonia and COVID-19 Adverse Events Among Patients With Type 2 Diabetes and Chronic Kidney Disease

A FIDELITY Pooled Secondary Analysis

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Abstract

IMPORTANCE Patients with chronic kidney disease and type 2 diabetes have a higher risk of developing pneumonia as well as an increased risk of severe COVID-19–associated adverse events and mortality. Therefore, the anti-inflammatory effects of mineralocorticoid receptor antagonists via blockade of the mineralocorticoid receptor may alter the risk of pneumonia and COVID-19–associated adverse events in patients with chronic kidney disease and type 2 diabetes.

OBJECTIVE To evaluate whether the selective, nonsteroidal mineralocorticoid receptor antagonist finerenone is associated with protection against pneumonia and COVID-19 adverse events in patients with type 2 diabetes and chronic kidney disease.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis used patient-level data from FIDELITY, a prespecified pooled analysis of 2 multicenter, double-blind, placebo-controlled, event-driven, phase 3 randomized clinical trials: FIDELIO-DKD and FIGARO-DKD, conducted between September 2015 and February 2021. Patients in FIDELIO-DKD or FIGARO-DKD with type 2 diabetes and chronic kidney disease (urine albumin to creatine ratio, 30-5000 mg/g, estimated glomerular filtration rate ≥25 mL/min/1.73 m^2) were assessed. Data were analyzed from May 15, 2021, to July 28, 2022.

EXPOSURE Patients were randomized to finerenone (10 or 20 mg once daily) or matching placebo.

MAIN OUTCOMES AND MEASURES The main outcomes were investigator-reported incidences of treatment-emergent infective pneumonia adverse events and serious adverse events (during and up to 3 days after treatment) and any COVID-19 adverse events.

RESULTS Of 13 026 randomized patients (mean [SD] age, 64.8 [9.5] years; 9088 [69.8%] men), 12 999 were included in the FIDELITY safety population (6510 patients receiving finerenone; 6489 patients receiving placebo). Over a median (range) treatment duration of 2.6 (0-5.1) years, finerenone was consistently associated with reduced risk of pneumonia and serious pneumonia vs placebo. Overall, 307 patients (4.7%) treated with finerenone and 434 patients (6.7%) treated with placebo experienced pneumonia (hazard ratio [HR], 0.71; 95% CI, 0.64-0.79; $P < .001$). Serious pneumonia occurred in 171 patients (2.6%) treated with finerenone and 250 patients (3.9%) treated with placebo (HR, 0.69; 95% CI, 0.60-0.79; $P < .001$). Incidence proportions of COVID-19 adverse events were 86 patients (1.3%) in the finerenone group and 118 patients (1.8%) in the placebo group (HR, 0.73; 95% CI, 0.60-0.89; $P = .002$).

(continued)

Key Points

Question Does mineralocorticoid receptor blockade with finerenone protect against pneumonia and COVID-19 adverse events (AEs) in patients with type 2 diabetes and chronic kidney disease?

Findings In this secondary analysis of 2 randomized clinical trials including 12 999 patients from 2 randomized clinical trials, the incidence of treatment-emergent pneumonia AEs and serious AEs was significantly lower with finerenone vs placebo. The rate of COVID-19 AEs was also significantly reduced with finerenone.

Meaning These findings suggest that finerenone treatment may be associated with protection from pneumonia and COVID-19 in patients with chronic kidney disease and type 2 diabetes; however, further clinical studies may be warranted.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE These findings suggest that mineralocorticoid receptor blockade with finerenone was associated with protection against pneumonia and COVID-19 adverse events in patients with type 2 diabetes and chronic kidney disease. Further clinical studies may be warranted.

TRIAL REGISTRATION ClinicalTrials.gov identifiers: FIDELIO-DKD: NCT02540993; FIGARO-DKD: NCT02545049

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Introduction

Pneumonia is a common cause of morbidity in individuals with chronic kidney disease (CKD) and is associated with increased hospitalization and mortality, as well as cardiovascular adverse events (AEs).[1] The risk of pneumonia is twice as high in individuals with CKD vs those without CKD and is independent of comorbid diabetes, cardiovascular disease (CVD), asthma, or chronic obstructive pulmonary disease.[1] In addition, CKD has been associated with an increased risk of severe disease and a higher mortality rate following SARS-CoV-2 infection[2]; diabetes is also a known major risk factor for COVID-19 morbidity and mortality.[3]

Angiotensin-converting enzyme 2 (ACE2) is the functional host receptor for the SARS-CoV-2 spike protein.[2,4] Implicated in the progression of COVID-19–associated acute respiratory syndrome,[4] ACE2 is a crucial component of the renin-angiotensin system and is widely distributed in the heart, kidneys, and lungs.[2,4] Renin-angiotensin system inhibitors and mineralocorticoid receptor antagonists (MRAs) increase ACE2 expression,[5] which led to early concerns that their use may enhance viral infectivity.[4] However, paradoxically, ACE2 has been demonstrated to be associated with protection against lung injury caused by acute respiratory distress syndrome.[4,6] This may be due to the second domain of ACE2, which generates angiotensin 1-7 that acts on the Mas receptor to reduce inflammation and preserve organ function.[5]

Preclinical data suggest that MRAs may attenuate pulmonary inflammation,[7] but no clinical studies have investigated the effect of MRAs on pneumonia or pneumonia-related death, to our knowledge.[8] Similarly, it has been suggested that the anti-inflammatory effects of MRAs, such as the steroidal MRA spironolactone, may confer protection against COVID-19.[9] Additionally, increased expression of protease nexin-1 by spironolactone may reduce the activity of furin and plasmin, reducing viral binding of the SARS-CoV-2 spike protein to ACE2 and effectively reducing the infectivity of COVID-19.[5,9]

Finerenone—a selective, nonsteroidal MRA—was evaluated in the FIDELIO-DKD and the FIGARO-DKD phase 3 studies in patients with type 2 diabetes and CKD.[10,11] The COVID-19 pandemic escalated during the later stages of conduct of these studies. The prespecified FIDELITY pooled efficacy and safety analysis of FIDELIO-DKD and FIGARO-DKD confirmed that finerenone was associated with reduced risk of kidney disease progression and improved cardiovascular outcomes.[12] In this study, we examine incidences of pneumonia and COVID-19 reported as AEs in FIDELITY, to evaluate whether finerenone treatment is associated with protection against pneumonia and COVID-19 in patients with type 2 diabetes and CKD.

Methods

This secondary analysis was conducted using individual patient-level data from 2 randomized clinical trials. Study protocols for both trials were approved by international review boards, independent ethics committees, and competent authorities according to national and international regulations. Both trials were conducted in accordance with the ICH Harmonised Tripartite Guideline for Good

Clinical Practice, and all study participants provided written informed consent before entering the studies. Trial protocols and statistical analysis plans for the FIGARO-DKD and FIDELIO-DKD and the FIDELITY pooled analysis study plan are available in Supplement 1. Details on the safety population in the FIDELITY pooled analysis are presented in the eFigure in Supplement 2. This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

The designs of the 2 multicenter, double-blind, placebo-controlled, event-driven, phase 3 randomized clinical trials, FIDELIO-DKD and FIGARO-DKD, as well as that of the FIDELITY pooled analysis have been described previously.[10-12] Briefly, FIDELITY was a prespecified analysis of 2 event-driven trials that assessed composite cardiovascular and renal outcomes, with trial completion in 2020 for FIDELIO-DKD and 2021 for FIGARO-DKD. In the FIDELITY analysis, the cardiovascular composite outcome included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; the renal composite outcome included kidney failure, a sustained 57% or greater decrease in estimated glomerular filtration rate (eGFR) from baseline over more than 4 weeks, or kidney death. Patients with type 2 diabetes and CKD (urine albumin to creatinine ratio 30-5000 mg/g and eGFR ≥25 mL/min/1.73 m^2) were treated with finerenone (10 or 20 mg once daily) or placebo. The titration scheme associated with finerenone treatment permitted dose adjustments dependent on kidney function and potassium levels and are fully described in the published parent trials.[10,11] All randomized participants who had received at least 1 dose of study medication were evaluated in the FIDELITY safety population. Patients self-reported race and ethnicity, categorized as Asian, Black, White, or other, including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, not reported, and patients identifying as multiple races. Race and ethnicity data were collected to allow for subsequent subanalyses to be performed to identify any differences in response among subpopulations.

Pneumonia, reported by investigators as an AE and diagnosed at the investigator's discretion without using specific diagnostic criteria, was analyzed using the Standardized *Medical Dictionary for Regulatory Activities* Query[13] (SMQ) term *infective pneumonia*, and COVID-19–related AEs were retrieved using the SMQ term *COVID-19* (narrow search). SMQs are validated, standard sets of terms that have undergone extensive review, testing, analysis, and expert discussion. Narrow terms are highly likely to represent the condition of interest. For pneumonia, treatment-emergent AEs were evaluated up to and including 3 days after treatment; for COVID-19, any AEs during the trials were considered.

Statistical Analysis

Cumulative incidence curves based on Aalen-Johansen estimates were calculated accounting for mortality from other causes as a competing risk. Stratified Cox models were fitted using the study stratification factors to reflect the design of the studies in the model. These included study, history of CVD, region, eGFR category at screening, and type of albuminuria at screening. These factors do not necessarily have an influence on the event of interest but account for differences in the different study strata. *P* values were interpreted as a measure of uncertainty. *P* values are based on 2-sided stratified log-rank test, and significance was set at $P < .05$. These post hoc analyses were performed with SAS software, version 9.4 (SAS Institute). Data were analyzed from May 15, 2021, to July 28, 2022.

Results

The FIDELITY prespecified pooled analysis included 13 026 randomized patients (mean [SD] age, 64.8 [9.5] years; 9088 [69.8%] men), with a median (IQR) follow-up of 3.0 (2.3-3.8) years. The baseline characteristics of patients in the FIDELITY analysis have been previously reported.[12] The baseline characteristics of patients who did and did not experience treatment-emergent pneumonia and COVID-19 AEs are presented overall in **Table 1** and by treatment group in the eTable in Supplement 2. In general, baseline characteristics in the subgroups of patients who experienced

treatment-emergent pneumonia were similar to the patients who did not experience an event; however, higher frequencies of chronic obstructive pulmonary disease, asthma, CVD, coronary artery disease, and obesity at baseline were observed in participants who experienced an event. For patients with COVID-19, there was a lower frequency of current smokers, a lower proportion of Asian patients, and a greater proportion of patients who were obese compared with those who did not experience an event (Table 1).

Over a median (range) treatment duration of 2.6 (0.0-5.1) years, a similar and consistent association of finerenone with reduced incidence of pneumonia and serious pneumonia events was observed compared with placebo overall (**Figure**). There was an early separation of cumulative incidence curves (at 3 months for pneumonia AEs and 6 months for serious AEs [SAEs]) (Figure).

Overall, 307 patients who received finerenone (4.7%; 1.88 events per 100 patient-years) reported treatment-emergent pneumonia compared with 434 patients in the placebo group (6.7%; 2.64 events per 100 patient-years; hazard ratio [HR], 0.71; 95% CI, 0.64-0.79; $P < .001$) (**Table 2**). In comparison, rates of other associated respiratory infections, such as nasopharyngitis (8.6% vs 8.9%), bronchitis (5.0% vs 5.1%), and influenza (3.9% vs 4.1%) were similar with finerenone vs placebo. Among patients with treatment-emergent pneumonia, the maximum intensity of pneumonia AEs in both the finerenone and placebo groups was most commonly reported as moderate (152 patients [49.5%] in the finerenone group; 222 patients [51.2%] in the placebo group), and most patients recovered from their worst outcome AE (238 patients [77.5%] in the finerenone group; 331 patients [76.3%] in the placebo group) (**Table 3**). Most patients with treatment-emergent

Table 1. Baseline Demographic and Clinical Characteristics of Patients Who Did and Did Not Experience Treatment-Emergent Pneumonia and COVID-19 AEs in the FIDELITY Population and COVID-19 in the FIGARO-DKD Population[a]

	Patients, No. (%)					
	FIDELITY pneumonia TE AE		FIDELITY COVID-19 AE		FIGARO-DKD COVID-19 AE[a]	
Characteristic	Yes (n = 741)	No (n = 12 258)	Yes (n = 204)	No (n = 12 795)	Yes (n = 198)	No (n = 7143)
Age, mean (SD), y	66.0 (9.31)	64.7 (9.54)	63.6 (9.4)	64.8 (9.5)	63.5 (9.5)	64.1 (9.9)
Sex						
Men	536 (72.3)	8535 (69.6)	138 (67.6)	8933 (69.8)	132 (66.7)	4966 (69.5)
Women	205 (27.7)	3723 (30.4)	66 (32.4)	3862 (30.2)	66 (33.3)	2177 (30.5)
Race						
Asian	172 (23.2)	2718 (22.2)	11 (5.4)	2879 (22.5)	11 (5.6)	1441 (20.2)
Black	26 (3.5)	495 (4.0)	11 (5.4)	510 (4.0)	11 (5.6)	247 (3.5)
White	510 (68.8)	8341 (68.0)	166 (81.4)	8685 (67.9)	160 (80.8)	5109 (71.5)
Other[b]	33 (4.5)	704 (5.7)	16 (7.8)	721 (5.6)	16 (8.1)	346 (4.8)
BMI, mean (SD)	31.7 (6.2)	31.3 (6.0)	33.5 (6.0)	31.2 (6.0)	33.5 (6.0)	31.4 (6.0)
Comorbidities						
COPD	90 (12.1)	697 (5.7)	12 (5.9)	775 (6.1)	11 (5.6)	451 (6.3)
Asthma	58 (7.8)	504 (4.1)	10 (4.9)	552 (4.3)	10 (5.1)	320 (4.5)
Cardiovascular disease	400 (54.0)	5524 (45.1)	105 (51.5)	5819 (45.5)	102 (51.5)	3222 (45.1)
Coronary artery disease	288 (38.9)	3702 (30.2)	72 (35.3)	3918 (30.6)	70 (35.4)	2221 (31.1)
Heart failure	71 (9.6)	935 (7.6)	18 (8.8)	988 (7.7)	16 (8.1)	554 (7.8)
Hypertension	723 (97.6)	11 816 (96.4)	202 (99.0)	12 337 (96.4)	196 (99.0)	6854 (96.0)
Obesity[c]	431 (58.2)	6609 (53.9)	145 (71.1)	6895 (53.9)	140 (70.7)	3910 (54.7)
eGFR, mean (SD), mL/min/1.73 m^2	56.1 (20.8)	57.7 (21.7)	65.4 (22.2)	57.5 (21.6)	66.1 (22.0)	67.9 (21.7)
UACR, median (IQR)	517 (207-1301)	514 (197-1136)	301 (86-659)	518 (203-1156)	301 (85-642)	309 (110-744)
Current smoker	131 (17.7)	1959 (16.0)	19 (9.3)	2071 (16.2)	18 (9.1)	1267 (17.7)

Abbreviations: AE, adverse event; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; TE, treatment-emergent; UACR, urine albumin to creatinine ratio.

[a] Due to the fact that most COVID-19 AEs occurred in FIGARO-DKD, FIGARO-DKD data are presented separately.

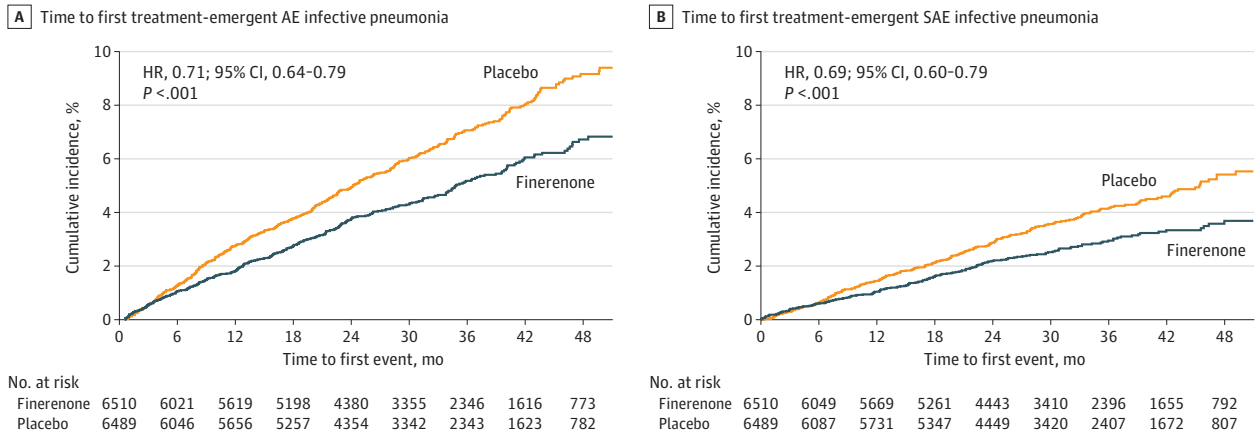
[b] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, not reported, and patients identifying as multiple races.

[c] Defined as BMI 30 or greater.

pneumonia did not receive a change in dose of study medication after a pneumonia AE (237 patients [77.2%] in the finerenone group; 340 patients [78.3%] in the placebo group), with drug withdrawal occurring in 6 patients (2.0%) in the finerenone group and 8 patients (1.8%) in the placebo group (Table 3). Overall, 286 patients (93.2%) in the finerenone group and 405 patients (93.3%) in the placebo group received concomitant medications for pneumonia, the most common of which were systemic anti-infectives (265 patients [86.3%] in the finerenone group; 388 patients [89.4%] in the placebo group) (**Table 4**).

Pneumonia was the most commonly reported SAE overall. Pneumonia SAEs affected 171 patients (2.6%; 1.03 events per 100 patient-years) in the finerenone group vs 250 patients (3.9%;

Figure. Time to Treatment-Emergent Infective Pneumonia



Data are cumulative incidence of Standardized MedDRA Query term *infective pneumonia* (narrow search) based on Aalen-Johansen estimates in the safety analysis set of the FIDELIO-DKD and FIGARO-DKD trials. AE indicates adverse event; HR, hazard ratio; SAE, serious adverse event.

Table 2. Treatment-Emergent Pneumonia and COVID-19 AEs in the FIDELITY and FIGARO-DKD Safety-Evaluable Populations

	Finerenone		Placebo			
Outcome	Patients, No. (%)	Events, No./100 PY	Patients, No. (%)	Events, No./100 PY	HR (95% CI)	*P* value[a]
FIDELITY						
No.	6510	NA	6489	NA	NA	NA
Pneumonia[b]						
AE	307 (4.7)	1.88	434 (6.7)	2.64	0.71 (0.64-0.79)	<.001
SAE	171 (2.6)	1.03	250 (3.9)	1.50	0.69 (0.60-0.79)	<.001
Fatal AE	10 (0.2)	0.06	13 (0.2)	0.08	0.78 (0.44-1.40)	.41
COVID-19[b]						
AE	86 (1.3)	0.43	118 (1.8)	0.59	0.73 (0.60-0.89)	.002
SAE	38 (0.6)	0.19	61 (0.9)	0.30	0.63 (0.47-0.83)	.001
Fatal AE	14 (0.2)	0.07	19 (0.3)	0.09	0.74 (0.46-1.21)	.23
FIGARO-DKD[c]						
No.	3683	NA	3658	NA	NA	NA
COVID-19[b]						
AE	83 (2.3)	0.66	115 (3.1)	0.93	0.72 (0.54-0.96)	.02
SAE	36 (1.0)	0.29	61 (1.7)	0.49	0.59 (0.39-0.90)	.01
Fatal AE	14 (0.4)	0.11	19 (0.5)	0.15	0.74 (0.37-1.49)	.40

Abbreviations: AE, adverse event; HR, hazard ratio; NA, not applicable; PY, patient-years; SAE, serious AE.

[a] *P* values are based on 2-sided stratified log-rank tests.

[b] Standardized MedDRA Query term *infective pneumonia* (narrow search) and *COVID-19* (narrow search).

[c] Because most COVID-19 AEs occurred in FIGARO-DKD, FIGARO-DKD data are presented separately.

1.50 events per 100 patient-years) receiving placebo (HR, 0.69; 95% CI, 0.60-0.79; $P < .001$) (Table 2). Among patients with pneumonia SAEs, most recovered from their worst outcome SAE (137 patients [80.1%] in the finerenone group; 191 patients [76.4%] in the placebo group), and most patients did not have their study medication dose changed because of a pneumonia SAE (107 patients [62.6%] in the finerenone group; 169 patients [67.6%] in the placebo group). Drug withdrawal occurred in 5 patients (2.9%) in the finerenone group and 8 patients (3.2%) in the placebo group. Fatal AEs were reported in 10 patients (5.8%) in the finerenone group and 13 patients (5.2%) in the placebo group. Of patients who experienced a pneumonia SAE, 160 patients (93.6%) in the finerenone group and 236 patients (94.4%) in the placebo group received concomitant treatment for pneumonia, with systemic anti-infectives as the most commonly used type of medication (144 patients [84.2%] in the finerenone group; 225 patients [90.0%] in the placebo group) (Table 4).

COVID-19 AEs were reported from January 2020 (index case), affecting very few patients in FIDELIO-DKD (6 patients) but more in FIGARO-DKD (198 patients). In total, a lower incidence of COVID-19 AEs was reported with finerenone vs placebo (86 patients [1.3%] vs 118 patients [1.8%]; HR, 0.73; 95% CI, 0.60-0.89; $P = .002$). Incidences of COVID-19 SAEs and fatal AEs are shown in Table 2. The proportion of patients experiencing a mild, moderate, or severe COVID-19 AE (as their most intense AE) was similar across finerenone and placebo groups (Table 3). The reported incidences of COVID-19 AEs and SAEs by worst outcome (by recovery status or fatality) and by action taken with the highest impact (drug withdrawn, interrupted, dose not changed, or unknown) are shown in Table 3.

Table 3. Treatment-Emergent Pneumonia and Any COVID-19 AEs and SAEs by Maximum Intensity, Worst Outcome, and Action Taken With the Highest Impact in the FIDELITY Safety-Evaluable Population

	Patients, No. (%)							
	Pneumonia[a]				COVID-19[a]			
	Finerenone (n = 6510)		Placebo (n = 6489)		Finerenone (n = 6510)		Placebo (n = 6489)	
Outcome	TE AE	TE SAE	TE AE	TE SAE	AE	SAE	AE	SAE
AE by maximum intensity[b]								
Mild	78 (1.2)	NA	94 (1.4)	NA	28 (0.4)	NA	34 (0.5)	NA
Moderate	152 (2.3)	NA	222 (3.4)	NA	27 (0.4)	NA	42 (0.6)	NA
Severe	77 (1.2)	NA	118 (1.8)	NA	31 (0.5)	NA	42 (0.6)	NA
Total	307 (4.7)	NA	434 (6.7)	NA	86 (1.3)	NA	118 (1.8)	NA
AE/SAE by worst outcome[c]								
Unknown	3 (<0.1)	1 (<0.1)	3 (<0.1)	2 (<0.1)	1 (<0.1)	0	2 (<0.1)	0
Recovered/resolved	238 (3.7)	137 (2.1)	331 (5.1)	191 (2.9)	56 (0.9)	14 (0.2)	70 (1.1)	31 (0.5)
Recovering/resolving	17 (0.3)	12 (0.2)	29 (0.4)	26 (0.4)	3 (<0.1)	3 (<0.1)	4 (<0.1)	2 (<0.1)
Recovered/resolved with sequelae	7 (0.1)	5 (<0.1)	7 (0.1)	5 (<0.1)	2 (<0.1)	2 (<0.1)	4 (<0.1)	4 (<0.1)
Not recovered/not resolved	32 (0.5)	6 (<0.1)	51 (0.8)	13 (0.2)	10 (0.2)	5 (<0.1)	19 (0.3)	5 (<0.1)
Fatal	10 (0.2)	10 (0.2)	13 (0.2)	13 (0.2)	14 (0.2)	14 (0.2)	19 (0.3)	19 (0.2)
Total	307 (4.7)	171 (2.6)	434 (6.7)	250 (3.9)	86 (1.3)	38 (0.6)	118 (1.8)	61 (0.9)
AE/SAE by action taken with the highest impact[d]								
Drug withdrawn	6 (<0.1)	5 (<0.1)	8 (0.1)	8 (0.1)	2 (<0.1)	2 (<0.1)	3 (<0.1)	3 (<0.1)
Drug interrupted	55 (0.8)	49 (0.8)	70 (1.1)	63 (1.0)	8 (0.1)	6 (<0.1)	15 (0.2)	12 (0.2)
Dose not changed	237 (3.6)	107 (1.6)	340 (5.2)	169 (2.6)	40 (0.6)	14 (0.2)	61 (0.9)	21 (0.3)
Not applicable	9 (0.1)	10 (0.2)	16 (0.2)	10 (0.2)	36 (0.6)	16 (0.2)	39 (0.6)	25 (0.4)

Abbreviations: AE, adverse event; NA, not applicable; SAE, serious AE; TE, treatment-emergent.

[a] SMQ, Standardized MedDRA Query term *infective pneumonia* (narrow search) and *COVID-19* (narrow search).

[b] Only the most severe intensity is counted for multiple occurrences of the same AE in each individual. A participant is counted only once within each preferred term or any primary system organ class.

[c] Number of participants with at least 1 such AE. Only the worst outcome is counted for multiple occurrences of the same AE in 1 individual.

[d] Per participant, only the action taken with highest impact is considered applying the following descending order: drug withdrawn, drug interrupted, dose reduced, dose not changed, NA, and unknown.

Discussion

In this secondary analysis of data from the FIDELITY pooled analysis, we observed a significant reduction in pneumonia AEs and SAEs associated with finerenone compared with placebo, with early onset of the associated protection based on cumulative incidence analyses. There was also a lower risk of COVID-19 AEs among patients who received finerenone. Pneumonia was the most commonly reported SAE in FIDELITY, highlighting that pneumonia is a significant source of morbidity in the CKD and type 2 diabetes population, as reported previously.[1] Although no between-group differences were observed in other associated respiratory infections, the striking reduction in risk of pneumonia observed in both independent studies might suggest that the propagation of pulmonary infection into lobar or bronchial consolidation may be reduced by finerenone.

Postulated mechanisms for protection against pneumonia and COVID-19 associated with finerenone include modulation of ACE2 expression, anti-inflammatory, and antifibrotic mechanisms.[14] Finerenone has demonstrated antifibrotic and anti-inflammatory effects in preclinical models.[7,15] Notably, in rodent models of idiopathic pulmonary fibrosis, finerenone reduced pulmonary proinflammatory and profibrotic markers in lung homogenate, with a higher efficacy than approved antifibrotic drugs (eg, pirfenidone, nintedanib).[15] Therefore, we propose that a combination of factors, including improvements in pulmonary inflammation and fibrosis, coupled with upregulation of ACE2 expression and amelioration of right-heart pressure and pulmonary congestion, are likely to lead to an improved pulmonary environment that is less susceptible to a propagation of pulmonary infection and inflammation. Additionally, antagonism of mineralocorticoid receptors on monocytes and macrophages by MRAs may block macrophage infiltration and accumulation of active macrophages,[16] which play a role in COVID-19–associated pulmonary tissue damage.[17]

Limitations

This study has some limitations. No specific adjudication criteria were used for pneumonia events (except hospitalizations and deaths); thus, some patients categorized as having pneumonia may

Table 4. Concomitant Medications for Treatment of TE AEs and TE SAEs for Pneumonia in the FIDELITY Safety-Evaluable Population With TE AEs

	Patients, No. (%)[a]			
	TE AEs		TE SAEs	
ATC class	Finerenone (n = 307)	Placebo (n = 434)	Finerenone (n = 171)	Placebo (n = 250)
Patients with concomitant treatment for pneumonia[b]	286 (93.2)	405 (93.3)	160 (93.6)	236 (94.4)
Not available[c]	19 (6.2)	21 (4.8)	8 (4.7)	5 (2.0)
Alimentary tract and metabolism	111 (36.3)	161 (37.1)	69 (40.4)	112 (44.8)
Anti-infectives for systemic use	265 (86.3)	388 (89.4)	144 (84.2)	225 (90.0)
Antineoplastic and immunomodulating agents	25 (8.1)	30 (6.9)	20 (11.7)	24 (9.6)
Antiparasitic products, insecticides, and repellants	4 (1.3)	5 (1.2)	4 (2.3)	3 (1.2)
Blood and blood-forming organs	39 (12.7)	64 (14.7)	35 (20.5)	55 (22.0)
Cardiovascular system	61 (19.9)	87 (20.0)	47 (27.5)	71 (28.4)
Dermatologicals	149 (48.5)	219 (50.5)	96 (56.1)	151 (60.4)
Genitourinary system and sex hormones	31 (10.1)	53 (12.2)	21 (12.3)	41 (16.4)
Musculoskeletal system	17 (5.5)	23 (5.3)	14 (8.2)	17 (6.8)
Nervous system	52 (16.9)	77 (17.7)	39 (22.8)	54 (21.6)
Respiratory system	133 (43.3)	195 (44.9)	77 (45.0)	125 (50.0)
Sensory organs	168 (54.7)	273 (62.9)	101 (59.1)	176 (70.4)
Systemic hormonal preparations (excluding sex hormones and insulins)	48 (15.6)	75 (17.3)	31 (18.1)	56 (22.4)
Various	60 (19.5)	107 (24.7)	35 (20.5)	69 (27.6)

Abbreviations: AE, adverse event; ATC, Anatomical Therapeutic Chemical; SAE, serious AE; TE, treatment-emergent.

[a] A patient is counted only once for each comedication class displayed. Per comedication, all ATC codes were considered, ie, 1 medication may be displayed in multiple ATC classes.

[b] Standardized MedDRA Query term *infective pneumonia* (narrow search).

[c] Not available refers to AEs marked as treated but without further information on comedication used.

represent misdiagnosed heart failure or pulmonary edema because diagnosis was done at the investigator's discretion and may vary across study sites. COVID-19 antigen and polymerase chain reaction testing were not widespread during study conduct and may have not been available, adequately sensitive, or readily performed. The number of COVID-19–associated AEs reported was low in FIDELIO-DKD because of the study timelines.

Conclusions

The findings of this secondary analysis suggest that mineralocorticoid receptor blockade with finerenone was associated with protection against pneumonia and COVID-19 AEs in patients with type 2 diabetes and CKD. Further research into elucidating if mineralocorticoid receptor blockade reduces pneumonia- and COVID-19–related complications in other patient groups would have significant medical implications, especially considering the limited treatment options for COVID-19 complications.

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Author Contributions: Dr Pitt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Pitt, Agarwal, Ruilope, Brinker, Joseph, Lawatscheck, Filippatos.

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Supervision: Pitt, Agarwal, Ruilope, Rossing, Joseph, Lawatscheck, Filippatos.

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Group Information: The FIDELIO-DKD and FIGARO-DKD Investigators appear in the eAppendix in Supplement 2.

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SUPPLEMENT 1.

Trial Protocols and Statistical Analysis Plans for FIDELIO-DKD and FIGARO-DKD Randomized Clinical Trials and the FIDELITY Pooled Analysis

SUPPLEMENT 2.

eFigure. Patient Recruitment Flowchart for FIDELITY Pooled Analysis

eTable. Baseline Demographics and Clinical Characteristics of Patients Who Did and Did Not Experience Treatment-Emergent Pneumonia and COVID-19 AEs in the FIDELITY Population and COVID-19 in the FIGARO-DKD Population by Treatment Group

eAppendix. Participating Countries and Investigators in FIDELIO-DKD and FIGARO-DKD

SUPPLEMENT 3.

Data Sharing Statement