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Finerenone versus spironolactone in patients with chronic kidney disease and type 2 diabetes: a target trial emulation

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The comparative effectiveness of finerenone and spironolactone in chronic kidney disease (CKD) with type 2 diabetes (T2D) remains unclear. Here we show, using a target trial emulation on global real-world data from TriNetX, outcomes among 2268 propensity score–matched adults with CKD (eGFR 15–60 mL/min/1.73 m^2) and T2D who initiated finerenone or spironolactone between July 2021 and September 2024. Over a median follow-up of 1.3 years, finerenone is associated with lower risks of major adverse cardiovascular events (adjust hazard ratio [aHR], 0.74; 95% CI, 0.58–0.94), major adverse kidney events (aHR, 0.47; 95% CI, 0.33–0.67), all-cause mortality (aHR, 0.31; 95% CI, 0.21–0.45), and hyperkalemia (17.2% vs. 26.4%; $P < 0.001$) compared with spironolactone. These findings suggest potential benefits of finerenone over spironolactone in reducing mortality and cardiorenal risk among patients with CKD and T2D.

Chronic kidney disease (CKD) is a major complication of type 2 diabetes (T2D) and a leading cause of kidney failure worldwide[1]. Patients with CKD and T2D have a substantially increased risk of cardiovascular disease and progressive kidney dysfunction, despite treatment with renin-angiotensin system (RAS) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors[2,3]. However, even with these therapies, a high residual risk of adverse outcomes remains, highlighting the need for additional treatment strategies.

Finerenone, a nonsteroidal mineralocorticoid receptor antagonist (MRA), has demonstrated cardiorenal benefits in patients with CKD and type 2 diabetes in the FIDELIO-DKD and FIGARO-DKD trials[4,5]. In contrast, spironolactone, a traditional and cost-effective steroidal MRA, has been shown to reduce proteinuria and blood pressure but is limited by a high incidence of hyperkalemia[6–9]. The BARACK-D trial evaluated spironolactone in patients with CKD and found limited cardiovascular benefits, with high discontinuation rates due to declines in estimated glomerular filtration rate (eGFR) and hyperkalemia[10].

Recently, steroidal agents such as spironolactone and eplerenone, along with the nonsteroidal agent finerenone, have been guideline-

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recommended for heart failure with reduced ejection fraction (HFrEF)[11] and are increasingly used in CKD[12], particularly in diabetic nephropathy[13]. However, direct comparisons of finerenone and spironolactone in real-world CKD and T2D populations remain scarce. Given their distinct pharmacological properties, further evaluation of their comparative effectiveness and safety is warranted in clinical practice. In this work, we conducted a target trial emulation using real-world electronic health records from the TriNetX network to compare the effectiveness and safety of finerenone and spironolactone in patients with CKD and T2D.

Results

Patient characteristics

Among the 18,314 patients who initiated finerenone or spironolactone between June 2021 and September 2024, 1345 were identified as eligible new users of finerenone (mean [SD] age, 68.5 [10.6] years; 799 [59.4%] male; 585 [43.5%] White), and 16,969 were eligible new users of spironolactone (mean [SD] age, 72.3 [11.1] years; 7435 [43.8%] male; 11,029 [65.0%] White). After propensity score matching (PSM), 1132 individuals were included in each group for outcome analyses (Table 1). The study cohort construction and exclusion criteria are shown in Fig. 1.

Prior to matching, the finerenone group had a higher prevalence of hyperuricemia compared with the spironolactone group. Conversely, the spironolactone group had a higher prevalence of anemia, cardiovascular and kidney comorbidities, other organ comorbidities, systemic disorders, sleep apnea, mood disorders, and lifestyle-related health hazards. After PSM, baseline characteristics were well balanced between the two groups.

Comparison of finerenone and spironolactone on outcome of interests

After a follow-up of 1.3 years (IQR, 0.8–1.5), treatment with finerenone was associated with a significantly lower risk of all-cause mortality compared with spironolactone (aHR, 0.31; 95% CI, 0.21–0.45; $P < 0.001$). A total of 35 patients (3.1%) in the finerenone group and 112 patients (9.9%) in the spironolactone group died. This corresponded to an absolute risk reduction (ARR) of 7% (95% CI, 5–9) and a number needed to treat (NNT) of 15 (95% CI, 11–21) (Table 2). The intention-to-treat survival probability for each treatment group is presented in Fig. 2. 112 patients (9.9%) in the finerenone group and 150 patients (13.3%) in the spironolactone group experienced MACE. Finerenone was associated with a significantly lower risk of MACE than spironolactone (aHR, 0.74; 95% CI, 0.58–0.94; $P = 0.013$), with an ARR of 3% (95% CI, 1%–6%) and a NNT of 29 (95% CI, 17–143) (Table 2). This association remained consistent across individual components, including acute myocardial infarction, cardiac arrest/ cardiogenic shock, and alternative MACE definitions (Supplementary Table 5). MAKE occurred in 46 patients (4.1%) in the finerenone group and 96 patients (8.5%) in the spironolactone group, with a lower hazard ratio in the finerenone group (aHR, 0.47; 95% CI, 0.33–0.67; $P < 0.001$). This corresponded to an ARR of 4% (95% CI, 2%–6%) and an NNT of 23 (95% CI, 16–42) (Table 2). The *E*-values for MACE (2.06), MAKE (3.68), and mortality (5.91) suggest that the observed associations are robust to unmeasured confounding (Table 2).

Secondary outcome

Patients receiving spironolactone experienced significantly more episodes of hyperkalemia. Hyperkalemia (potassium ≥5.5 mmol/L) occurred in 26.4% of patients receiving spironolactone and 17.2% of those receiving finerenone ($P < 0.001$). Hyperkalemia (potassium ≥6.0 mmol/L) was observed in 10.2% of the spironolactone group and 5.9% of the finerenone group ($P < 0.001$). Severe hyperkalemia with potassium ≥6.5 mmol/L occurred in 3.9% of the spironolactone group and 2.1% of the finerenone group ($P = 0.014$) (Supplementary Table 6).

Subgroup and sensitivity analyses

The association between finerenone use and a lower risk of the primary outcomes remained consistent across subgroups stratified by age, sex, HbA1c level (≥7% vs <7%), kidney function (eGFR ≥45, 30–44, and <30 mL/min/1.73 m^2), proteinuria (UPCR ≥ 300 vs <300 mg/g), heart failure status, concurrent SGLT2 inhibitor use, RAS inhibitor use, and enrollment year. Notably, the association with lower mortality was more pronounced among patients receiving RAS inhibitors (p for interaction = 0.048), and the association with lower MAKE risk was stronger among those enrolled in 2024 or later (p for interaction <0.001). No significant effect modification was observed in other subgroups (p for interaction >0.05 for all) (Fig. 3).

Treatment persistence was modest overall, with 49.0% of patients remaining on finerenone and 55.5% on spironolactone at 6 months, declining to 33.8% and 28.3% at 12 months, respectively. In landmark analyses restricted to patients with continued treatment at 3 and 6 months, finerenone was consistently associated with lower risks of MACE, MAKE, and all-cause mortality compared with spironolactone (Supplementary Table 7). Additional analyses performed before PSM, censoring events within the first 30 days of treatment initiation, restricting the cohort to those with documented drug doses (10 mg for finerenone, 25 mg for spironolactone), excluding patients who switched to other MRAs, and limited to patients with complete laboratory data also supported the robustness of our findings (Supplementary Tables 8 and 9).

Negative outcome analysis

In the negative outcome analysis of overall cancer risk, patients with a history of cancer at treatment initiation were excluded. No significant difference in the risk of de novo cancer was observed between the two treatment groups (Supplementary Table 6).

Discussion

In this real-world cohort study emulating a randomized clinical trial, finerenone use in patients with CKD and T2D was associated with a lower risk of all-cause mortality, MACE, and MAKE compared with spironolactone, with a median follow-up of 1.3 years (IQR, 0.8–1.5). Notably, the combination of finerenone with RAS inhibitors was associated with a significant reduction in the risk of MACE. Furthermore, clinical use of finerenone after 2024 was linked to a decreased risk of MAKE. Additionally, in this new-user intention-to-treat study, treatment with finerenone was associated with a lower incidence of hyperkalemia compared with spironolactone.

To our knowledge, this is the first study to head-to-head compare the effectiveness of finerenone versus spironolactone in a real-world cohort of patients with CKD and T2D using a target trial emulation approach. Previous randomized trials, such as FIGARO-DKD and FIDELIO-DKD, have demonstrated the cardiovascular and kidney benefits of finerenone in this population, with the pooled FIDELITY analysis confirming its ability to delay CKD progression[4,5,14]. Despite differences in baseline characteristics and follow-up duration, the 9.9% MACE incidence and 3.1% mortality we observed over 1.3 years are broadly consistent with those reported in the FIDELIO-DKD trial, reinforcing the external validity of our real-world findings. In contrast, spironolactone, commonly used for CKD-related hypertension and proteinuria, may be limited by a higher incidence of hyperkalemia. The BARACK-D trial did not identify significant cardiovascular benefits associated with spironolactone use in patients with CKD, likely due to its frequent discontinuation owing to safety concerns, even at low doses[10]. Furthermore, low-dose spironolactone users did not demonstrate a significant benefit in slowing renal function decline over the study period[10]. In a post hoc analysis of the FIDELITY-TRH and AMBER studies, finerenone was associated with a lower risk of hyperkalemia and treatment discontinuation compared with spironolactone in patients with treatment-resistant hypertension and CKD[15].

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Table 1 | Baseline characteristics of patients with chronic kidney disease and type 2 diabetes initiating finerenone or spironolactone, before and after propensity score matching

Characteristic	Before PSM, No. (%)			After PSM, No. (%)		
	Finerenone group (*n* = 1345)	Spironolactone group (*n* = 16,969)	SMD	Finerenone group (*n* = 1132)	Spironolactone group (*n* = 1132)	SMD
Age, mean (SD), years	68.5 (10.6)	72.3 (11.1)	0.356	68.9 (10.4)	68.9 (12.2)	0.002
Sex, %						
Male	799 (59.4)	7435 (43.8)	0.316	641 (56.6)	644 (56.9)	0.005
Female	546 (40.6)	9521 (56.1)	0.314	491 (43.4)	487 (43.0)	0.007
Unknown sex	0 (0)	13 (0.1)	0.039	0 (0)	1 (0.1)	0.042
Ethnicity						
Not Hispanic or Latino	1115 (82.9)	13,245 (78.1)	0.122	923 (81.5)	910 (80.4)	0.029
Hispanic or Latino	93 (6.9)	770 (4.5)	0.102	77 (6.8)	77 (6.8)	<0.001
Unknown ethnicity	137 (10.2)	2954 (17.4)	0.211	132 (11.7)	145 (12.8)	0.035
Race						
White	585 (43.5)	11,029 (65.0)	0.442	543 (48.0)	516 (45.6)	0.048
Black or African American	173 (12.9)	3,399 (20.0)	0.194	167 (14.8)	180 (15.9)	0.032
Asian	393 (29.2)	743 (4.4)	0.704	248 (21.9)	254 (22.4)	0.013
Native Hawaiian	26 (1.9)	90 (0.5)	0.127	19 (1.7)	16 (1.4)	0.021
Unknown race	168 (12.5)	1708 (10.1)	0.076	155 (13.7)	166 (14.7)	0.029
Comorbidities						
Essential Hypertension	1100 (81.8)	14,141 (83.3)	0.041	935 (82.6)	921 (81.4)	0.032
Ischemic heart diseases	417 (31.0)	8,602 (50.7)	0.409	375 (33.1)	377 (33.3)	0.004
Heart failure	263 (19.6)	10,585 (62.4)	0.967	258 (22.8)	255 (22.5)	0.006
Cerebrovascular diseases	141 (10.5)	2,692 (15.9)	0.160	126 (11.1)	120 (10.6)	0.017
Peripheral vascular diseases	137 (10.2)	2,170 (12.8)	0.082	125 (11.0)	112 (9.9)	0.038
Atrial fibrillation and flutter	169 (12.6)	6,443 (38.0)	0.611	164 (14.5)	149 (13.2)	0.038
Acute kidney failure	252 (18.7)	5,331 (31.4)	0.296	230 (20.3)	227 (20.1)	0.007
COPD	93 (6.9)	3889 (22.9)	0.461	87 (7.7)	83 (7.3)	0.013
Liver diseases	110 (8.2)	3075 (18.1)	0.297	105 (9.3)	96 (8.5)	0.028
Neoplasms	324 (24.1)	5175 (30.5)	0.144	288 (25.4)	296 (26.1)	0.016
Anemia	437 (32.5)	6785 (40.0)	0.156	384 (33.9)	370 (32.7)	0.026
Systemic connective tissue disorders	23 (1.7)	581 (3.4)	0.109	21 (1.9)	13 (1.1)	0.058
Hyperuricemia	65 (4.8)	338 (2.0)	0.157	53 (4.7)	38 (3.4)	0.068
Sleep apnea	233 (17.3)	4959 (29.2)	0.284	215 (19.0)	216 (19.1)	0.002
Lifestyle factors						
Depressive episode	109 (8.1)	2970 (17.5)	0.284	104 (9.2)	89 (7.9)	0.047
Anxiety disorders	126 (9.4)	3294 (19.4)	0.289	116 (10.2)	104 (9.2)	0.036
Nicotine dependence	66 (4.9)	1626 (9.6)	0.181	63 (5.6)	56 (4.9)	0.028
Alcohol related disorders	14 (1.0)	515 (3.0)	0.141	14 (1.2)	14 (1.2)	<0.001
SES and psychosocial-related health hazards	22 (1.6)	700 (4.1)	0.149	22 (1.9)	22 (1.9)	0.006
Diabetic complications						
Ophthalmic	202 (15.0)	1740 (10.3)	0.144	169 (14.9)	159 (14.0)	0.025
Neurologic	326 (24.2)	4469 (26.3)	0.048	283 (25.0)	294 (26.0)	0.022
Circulatory	201 (14.9)	2742 (16.2)	0.034	173 (15.3)	152 (13.4)	0.053
Medications						
Insulin	578 (43.0)	9646 (56.8)	0.280	503 (44.4)	509 (45.0)	0.011
Metformin	396 (29.4)	4452 (26.2)	0.072	329 (29.1)	333 (29.4)	0.008
GLP-1RA	339 (25.2)	1929 (11.4)	0.364	264 (23.3)	266 (23.5)	0.004
SGLT2 inhibitors	701 (52.1)	3742 (22.1)	0.655	510 (45.1)	516 (45.6)	0.011
RAS inhibitors	931 (69.2)	9814 (57.8)	0.238	757 (66.9)	753 (66.5)	0.077
Calcium channel blocker	644 (47.9)	7668 (45.2)	0.054	532 (47.0)	549 (48.5)	0.030
Beta-blocker	620 (46.1)	11,724 (69.1)	0.478	552 (48.8)	584 (51.6)	0.057
Aspirin	290 (21.6)	7007 (41.3)	0.435	260 (23.0)	263 (23.2)	0.006
Anticoagulants	310 (23.0)	10,412 (61.4)	0.842	301 (26.6)	297 (26.2)	0.008
HMG-CoA reductase	884 (65.7)	11,124 (65.6)	0.004	731 (64.6)	733 (64.8)	0.004
Allopurinol	178 (13.2)	2034 (12.0)	0.038	144 (12.7)	138 (12.2)	0.016

Table 1 (continued) | Baseline characteristics of patients with chronic kidney disease and type 2 diabetes initiating finerenone or spironolactone, before and after propensity score matching

Characteristic	Before PSM, No. (%)			After PSM, No. (%)		
	Finerenone group (*n* = 1345)	Spironolactone group (*n* = 16,969)	SMD	Finerenone group (*n* = 1132)	Spironolactone group (*n* = 1132)	SMD
Laboratory and vital signs measurements						
SBP, mean (SD), mmHg						
≥130 mmHg	992 (73.8)	13,076 (77.1)	0.077	830 (73.3)	836 (73.9)	0.012
<130 mmHg	77 (5.7)	1,048 (6.2)	0.021	60 (5.3)	58 (5.1)	0.029
No measurement	276 (20.5)	2845 (16.8)	0.10	242 (21.4)	238 (21.0)	0.009
HbA1c, mean (SD), %						
≥7 %	747 (55.5)	7323 (43.2)	0.250	618 (54.6)	620 (54.8)	0.004
<7 %	403 (30.0)	5960 (35.1)	0.109	334 (29.5)	346 (30.6)	0.024
No measurement	195 (14.5)	3686 (21.7)	0.18	180 (15.9)	166 (14.7)	0.029
BMI, mean (SD), kg/m^2						
≥30 kg/m^2	525 (39.0)	8,787 (51.8)	0.258	467 (41.3)	466 (41.2)	0.002
<30 kg/m^2	473 (35.2)	3,933 (23.2)	0.266	346 (30.6)	355 (31.4)	0.017
No measurement	347 (25.8)	4,249 (25.0)	0.018	319 (28.2)	311 (27.5)	0.009
eGFR, mL/min/1.73m^2						
≥45 mL/min/1.73m^2	212 (15.8)	4185 (24.7)	0.223	191 (16.9)	174 (15.4)	0.041
30-44 mL/min/1.73m^2	616 (45.8)	7348 (43.3)	0.050	521 (46.0)	521 (46.0)	<0.001
<30 mL/min/1.73m^2	517 (38.4)	5436 (32.0)	0.134	420 (37.1)	437 (38.6)	0.031
UPCR, mg/g						
≥300 mg/g	350 (26.0)	955 (5.6)	0.528	232 (20.5)	243 (21.5)	0.024
30-300 mg/g	130 (9.7)	596 (3.5)	0.250	97 (8.6)	107 (9.5)	0.031
<30 mg/g	96 (7.1)	779 (4.6)	0.207	93 (8.2)	81 (7.2)	0.036
No measurement	769 (57.2)	14,639 (86.3)	0.588	710 (62.7)	701 (61.9)	0.017
LDL, mg/dL						
≥160 mg/dL	67 (5.0)	518 (3.1)	0.098	54 (4.8)	54 (4.8)	<0.001
100–160 mg/dL	305 (22.7)	2764	(16.3)	0.162	243 (21.5)	242 (21.4)
<100 mg/dL	663 (49.3)	7548 (44.5)	0.096	538 (47.6)	552 (48.8)	0.024
No measurement	310 (23.0)	6139 (36.2)	0.29	297 (26.3)	284 (25.1)	0.027
Total cholesterol, mg/dL						
≥240 mg/dL	83 (6.2)	669 (3.9)	0.102	66 (5.8)	74 (6.5)	0.029
200–240 mg/dL	176 (13.1)	1360 (8.0)	0.166	141 (12.5)	121 (10.7)	0.055
<200 mg/dL	765 (56.9)	8542	(50.3)	0.133	631 (55.7)	628 (55.5)
No measurement	321 (23.9)	6398 (37.7)	0.30	294 (26.0)	309 (27.3)	0.010
Potassium, mEq/L						
4.5–5.0 mEq/L	944 (70.2)	11,347 (66.9)	0.071	783 (69.2)	748 (66.1)	0.066
<4.5 mEq/L	401 (29.8)	5622 (33.1)	0.071	349 (30.8)	384 (33.9)	0.066

BMI body mass index, *CCB* calcium channel blocker, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *HbA1c* glycated hemoglobin, *HMG-CoA* hydroxymethylglutaryl-CoA, *LDL* low-density lipoprotein, *PSM* propensity score matching, *RAS* renin-angiotensin system, *SBP* systolic blood pressure, *SES* socioeconomic status, *SMD* standardized mean difference, *SGLT2* sodium-glucose cotransporter-2, *UPCR* urine protein and creatinine ratio.

Both steroidal and non-steroidal MRAs mitigate endothelial dysfunction, oxidative stress, and albuminuria via aldosterone blockade[8,16–18]. Spironolactone has been shown to reduce left ventricular (LV) mass, improve arterial stiffness, and enhance LV function in early CKD[19,20]. However, spironolactone use is often limited by early discontinuation, with nearly two-thirds stopping treatment within 6 months in the BARACK-D trial[10], compared to lower discontinuation rates (~27–29%) over full follow-up in finerenone trials[4,5]. In our real-world study, treatment persistence between 6 and 12 months was higher in the finerenone group (33.8%) compared to spironolactone (28.3%). This pattern may reflect better long-term tolerability in patients with finerenone.

Hyperkalemia remains a key limitation of MRAs therapy in CKD management. Discontinuation or down-titration of MRAs, due to hyperkalemia, is associated with significantly increased risks of adverse outcomes in patients with CKD and heart failure. The *BIOSTAT-CHF* and *Swedish HF* registries previously found that the hyperkalemia itself was not directly linked to adverse outcomes—instead, it marked suboptimal therapy that led to worse prognosis[21,22]. In our study, finerenone was associated with a lower risk of hyperkalemia compared with spironolactone, which aligns with prior research[15]. Before matching, mean serum potassium was marginally higher in participants treated with finerenone than in those given spironolactone, a disparity that likely reflects clinicians' preference for finerenone in patients with hyperkalemia liability. This imbalance was eliminated after matching, and finerenone still conferred a lower incidence of treatment-emergent hyperkalemia than spironolactone. Our specificity analyses yielded consistent findings, with finerenone being associated with greater benefit than spironolactone, particularly in the lower risk of cardiac arrest. This observation aligns with the lower incidence of hyperkalemia-related sudden cardiac death observed in the finerenone group. These findings support the potential role of finerenone as an alternative to spironolactone in the management of patients with CKD and type 2 diabetes, particularly among those at increased risk of potassium dysregulation.

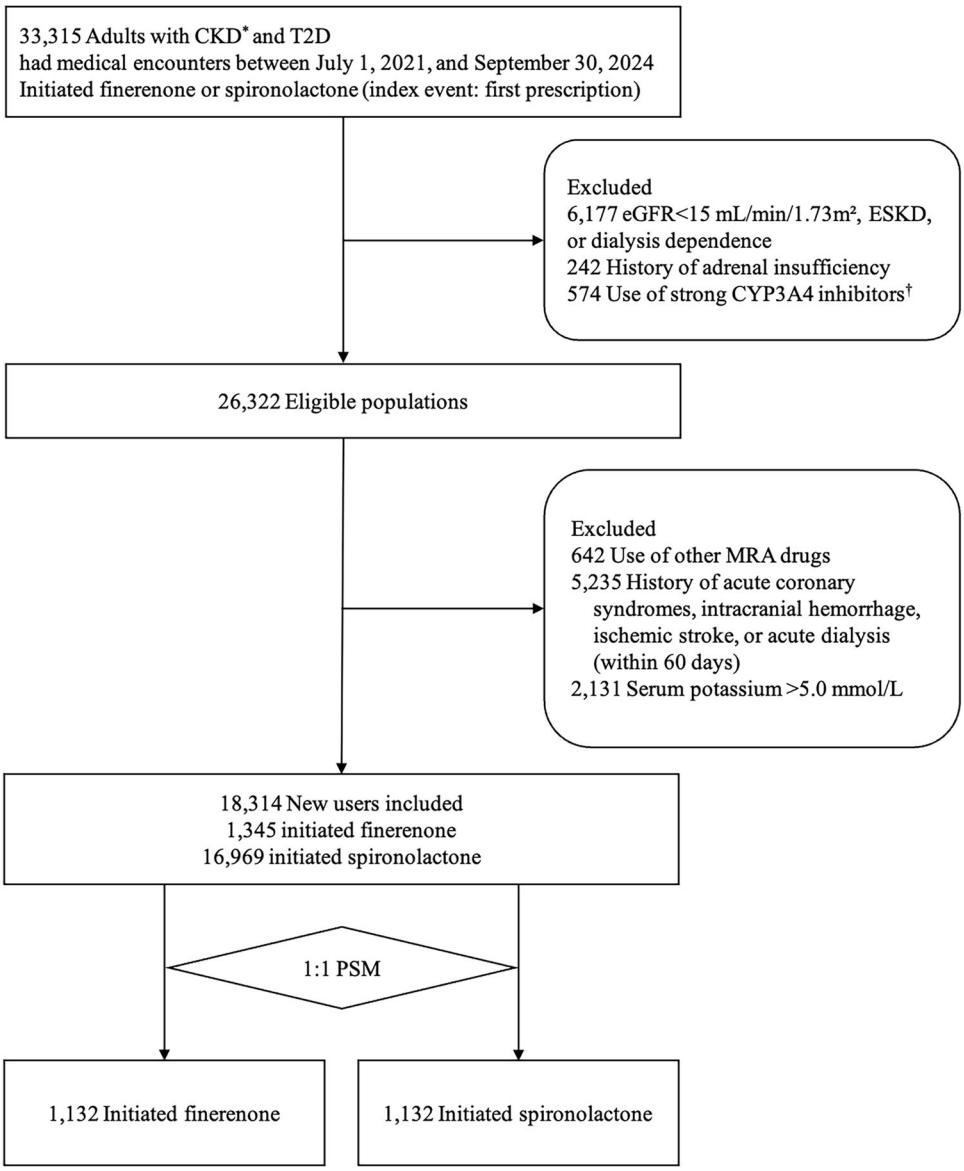

Fig. 1 | Study cohort construction and exclusion criteria. *CKD was defined by two eGFR values < 60 mL/min/1.73 m² (using the Modification of Diet in Renal Disease Study [MDRD] formula), separated by at least 90 days. †Strong CYP3A4 inhibitors, for example ketoconazole, clarithromycin, etc. CKD chronic kidney disease, CYP3A4 cytochrome P450 3A4, ESKD end stage kidney disease, ICH intracranial hemorrhage, MRA mineralocorticoid receptor antagonist, PSM propensity score matching.

Table 2 | Comparison of primary outcomes between finerenone and spironolactone: intention-to-treat analysis

Outcomes	No. of Patients with outcome		aHR (95% CI)	*P* value	*E*-value (upper CI)	ARR (95% CI)	NNT (95% CI)
	Finerenone (*n* = 1132)	Spironolactone (*n* = 1132)					
MACE	112	150	0.74 (0.58–0.94)	0.013	2.06 (1.33)	0.03 (0.01–0.06)	29 (17–143)
MAKE	46	96	0.47 (0.33–0.67)	<0.001	3.68 (2.35)	0.04 (0.02–0.06)	23 (16–42)
All-cause mortality	35	112	0.31 (0.21–0.45)	<0.001	5.91 (3.83)	0.07 (0.05–0.09)	15 (11–21)

P values were calculated using a two-sided log-rank test. Exact *p* values are provided where available; otherwise, *p* values are reported as <0.001 when below this threshold. No adjustments were made for multiple comparisons.
aHR adjust hazard ratio, *CI* confidence interval, *MACE* major adverse cardiac events, *MAKE* major adverse kidney events.

Furthermore, the observed association between finerenone and reduced mortality and cardiorenal outcomes may be partly attributed to its distinct pharmacological properties beyond treatment persistence and lower hyperkalemia risk[14]. Finerenone has distinct pharmacological properties, including inhibition of pro-inflammatory and pro-fibrotic pathways via suppression of serum/glucocorticoid-regulated kinase 1 (Sgk1) activation and prevention of cofactor recruitment to mineralocorticoid receptors[23–25]. Finerenone shows

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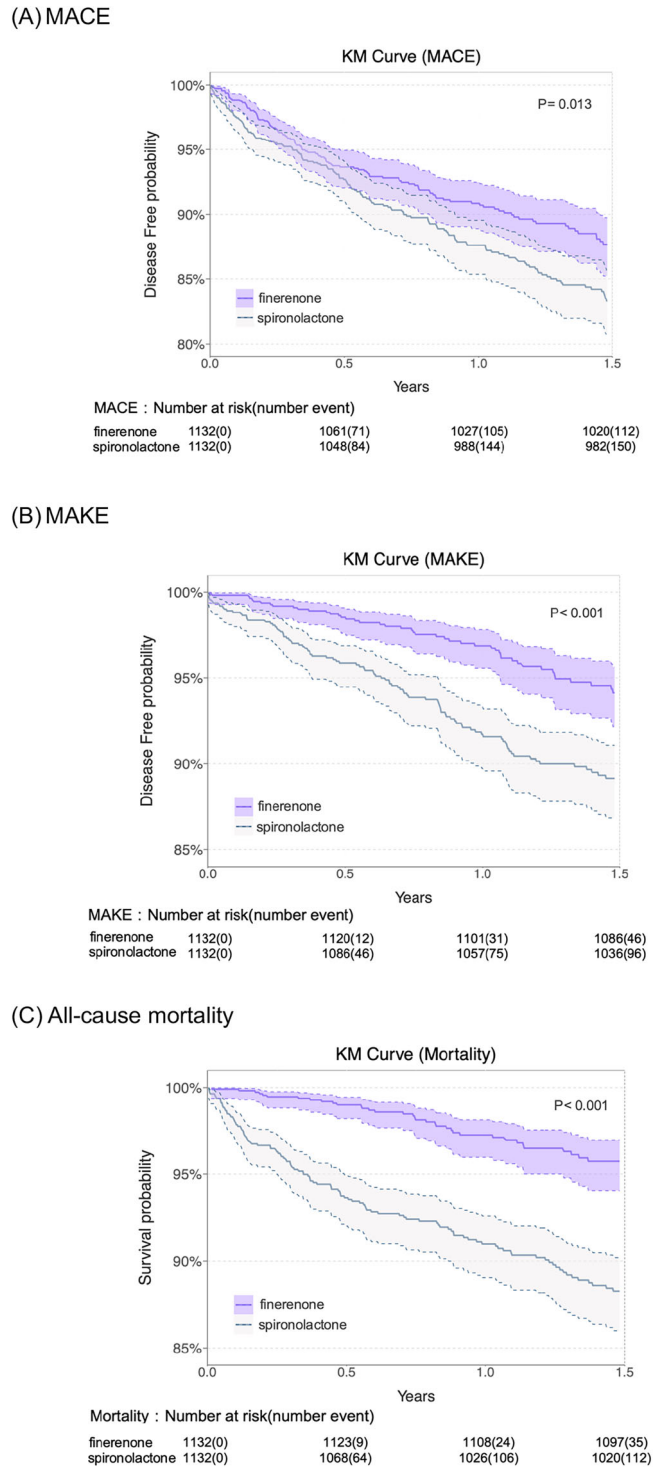

Fig. 2 | Cumulative incidence of study outcomes in patients with chronic kidney disease and type 2 diabetes. A MACE. **B** MAKE. **C** All-cause mortality. Kaplan–Meier curves show estimated survival/event-free probabilities for each treatment group (centre), with shaded areas indicating 95% confidence intervals (error bands). The number at risk and the number of events at each time point are shown below each panel. Sample sizes for both finerenone and spironolactone groups are $n = 1132$, with each patient representing an independent biological replicate. *P* values were calculated using a two-sided log-rank test. Exact *p* values are provided where available; otherwise, *p* values are reported as <0.001 when below this threshold. No adjustments were made for multiple comparisons. Source data are provided as a Source data file. MACE major adverse cardiac events, MAKE major adverse kidney events.

superior antifibrotic effects in the heart and kidneys, slowing CKD progression in patients with diabetes[15]. These pharmacological distinctions provide a potential explanation for our findings and highlight finerenone's role as a more targeted therapeutic option in CKD and T2D[23].

The low NNT for mortality (15) from our study underscores the potential benefit even over short-term follow-up in this high-risk population. Furthermore, finerenone appears to act synergistically with RAS inhibitors, providing a more comprehensive strategy for managing cardiorenal complications in T2D. A meta-analysis demonstrated that finerenone, when combined with RAS inhibitors, improved cardiovascular and kidney outcomes and reduced the risk of hyperkalemia compared with than traditional MRAs such as spironolactone[26]. Clinically, this dual blockade has been shown to enhance cardiorenal outcomes: the FIDELIO-DKD and FIGARO-DKD trials reported that the addition of finerenone to optimized RAS blockade significantly reduced rates of MACE, particularly hospitalizations for heart failure and cardiovascular mortality[4,5,14].

This study has several limitations. First, as a retrospective analysis, residual confounding cannot be fully excluded despite the rigorous adjustments made using propensity score matching and the target trial framework. However, *E*-value analysis suggests that an unmeasured confounder would be unlikely to account for the observed associations. Indication bias remains a limitation, as finerenone was more frequently prescribed to patients with lower eGFR and higher potassium levels, though we adjusted for complications and cardiorenal risk factors associated with diabetes as proxy of disease severity, which likely mitigated potential bias. However, the use of a target trial emulation approach strengthens the validity of causal inferences by systematically mitigating key sources of bias, including immortal time bias, selection bias, and depletion of susceptible bias. Second, the reliance on EHRs and standardized coding systems, including the International Classification of Diseases, 10th Revision (ICD-10), may introduce ascertainment bias due to potential misclassification or incomplete capture of events. While negative control outcome was used to assess potential systemic bias, overdiagnosis, underdiagnosis, or misclassification cannot be fully excluded. Third, the relatively short follow-up period of 1.3 years, reflecting the recent approval of finerenone, limits our ability to draw definitive conclusions on long-term efficacy and safety, which are critical in managing chronic diseases like CKD. Fourth, treatment adherence over time could not be fully assessed; exposure was defined at baseline, and dynamic changes such as discontinuation or switching were not captured. However, treatment persistence and landmark sensitivity analyses supported the robustness of our findings among sustained users, although residual misclassification was possible. Additionally, the reasons for treatment discontinuation, such as hyperkalemia or other adverse events, were not captured in the database, limiting further insight into discontinuation patterns. Fifth, the predominance of spironolactone 25 mg and finerenone 10 mg prescriptions limited our ability to evaluate dose–response effects. A dose-restricted sensitivity analysis confined to these common doses corroborated the primary findings. Moreover, a notable portion of patients had missing or unrecorded MRA dosing data, further restricting detailed dose stratification. Sixth, missing laboratory data, especially proteinuria (UPCR), is a common limitation of EHR studies. High UPCR missingness may underestimate proteinuria prevalence and affect generalizability. Finally, CKD was defined based on two eGFR measurements at least 90 days apart, which may have inadvertently included patients with transient declines due to acute kidney injury. However, this algorithm has been previously validated for CKD stage 3 or greater[27].

Ongoing clinical trials, such as FIND-CKD (NCT05047263) and CAPTIVATE (NCT06058585), will further elucidate the efficacy of finerenone in a broader CKD population, including individuals without diabetes. Additionally, the CONFIDENCE trial (NCT05254002) will

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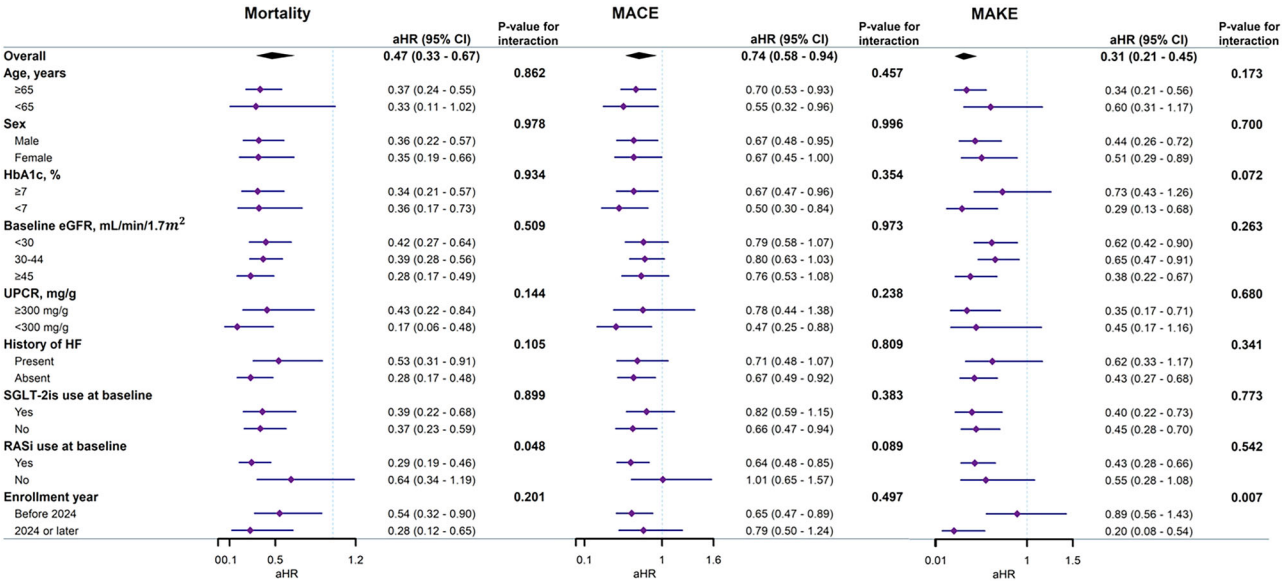

Fig. 3 | Adjusted hazard ratios for primary outcomes across prespecified subgroups. Points represent the estimated hazard ratio (measure of centre) for each subgroup, and horizontal lines represent the corresponding 95% confidence intervals (error bars). Sample sizes for both finerenone and spironolactone groups are $n = 1132$, with each patient representing an independent biological replicate. *P* values for interaction were derived from likelihood-ratio χ^2 tests comparing Cox models with versus without the treatment × subgroup interaction terms in the PS-matched cohort. Exact *p* values are provided where available; otherwise, *p* values are reported as <0.001 when below this threshold. No adjustments were made for multiple comparisons. Source data are provided as a Source data file. eGFR estimated glomerular filtration rate, HbA1c glycated hemoglobin, HF heart failure, MACE major adverse cardiac events, MAKE major adverse kidney events, RAS renin-angiotensin system, SGLT2 sodium-glucose cotransporter-2, UPCR urine protein and creatinine ratio.

evaluate the potential benefits of combining MRAs with SGLT2 inhibitors, particularly in managing potassium homeostasis and improving long-term clinical outcomes in patients with CKD. As finerenone moves toward broader clinical adoption, its higher cost relative to spironolactone warrants careful consideration. Although modeling studies suggest that finerenone may be cost-effective in CKD and T2D[28–32], cost-effectiveness data for spironolactone remain limited[10]. Rigorous cost-utility analyses in resource-limited settings are therefore required before widespread adoption.

In this real-world cohort study emulating a randomized clinical trial, use of finerenone in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) was associated with a significantly lower risk of all-cause mortality, as well as cardiovascular and kidney events, compared with spironolactone. Finerenone use was also linked to a reduced incidence of hyperkalemia, a common safety concern with MRA therapy. These findings suggest that finerenone may offer improved clinical outcomes and a more favorable safety profile in this high-risk population. However, confirmation through prospective, long-term randomized clinical trials is needed to validate these real-world observations and inform optimal treatment strategies in patients with CKD and T2D.

Methods

The study adhered to the ethical principles of the Declaration of Helsinki[33] and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. Ethical approval for this study was obtained from the Institutional Review Board of Chi Mei Hospital (approval number: 11210- E01). In addition, all participating healthcare organizations contributing data to the TriNetX Research Network had obtained institutional review board (IRB) or ethics committee approval to share de-identified data. The use of de-identified, aggregated data was deemed exempt from informed consent by the Western Institutional Review Board. This exemption is based on the TriNetX platform's data de-identification process, which complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and General Data Protection Regulation (GDPR) standards. The data are formally certified by a qualified expert as de-identified, contain no protected health information (PHI), and are presented only as aggregated summaries, thus, the research is considered non-human subjects research and exempt from informed consent requirements.

Data source

This study used data from the TriNetX platform, which aggregates electronic health records (EHRs) from the Global Collaborative Network, comprising 146 healthcare organizations (HCOs). These HCOs span 21 countries across the Americas, Europe/Middle East/Africa (EMEA), and Asia-Pacific (APAC) regions, including the United States, United Kingdom, Germany, France, Israel, Japan, Taiwan, and Australia. The available EHR data include patient demographics (including sex as recorded in the individual's EHR), diagnoses, medications, procedures, laboratory tests, genomics, visits, and details related to socioeconomic factors and lifestyle. Race and ethnicity are recorded separately in TriNetX, consistent with clinical documentation standards in the United States and other participating regions. This network encompasses both insured and uninsured patients from a range of clinical settings, including hospitals, primary care units, and specialty clinics[34–42].

Target trial specification and emulation

The target trial emulation framework was used to design and analyze this observational study, replicating an RCT structure using observational data[43,44]. This framework has been widely applied in clinical research, particularly in studies on CKD[45,46]. To emulate randomization, the finerenone and spironolactone groups were propensity-score matched for these covariates[47]. Details of the target trial specification, including eligibility criteria, treatment strategies, outcomes, and analysis approach, are provided in Supplementary Table 1 and Supplementary Fig. 1.

Eligibility criteria

The target trial emulation included adults aged ≥18 years with CKD and T2D who had medical encounters between July 2021 and September 2024. This study period was selected as finerenone was first approved by

the US FDA in July 2021. Incident CKD was defined as two eGFR values < 60 mL/min/1.73 m², measured at least 90 days apart, using the Modification of Diet in Renal Disease Study (MDRD) formula. Patients were grouped based on the first prescription (new users) of either finerenone or spironolactone, marking the baseline or index event. Eligible patients had no history of either MRAs use in the preceding 6 months before index event. Exclusion criteria included prior eGFR values < 15 mL/min/1.73 m², end-stage renal disease (ESRD), or recent events such as acute coronary syndromes, stroke, cardiac arrest, cardiogenic shock, or ever dialysis within 60 days of the index prescription. Other exclusions included medical contraindications (e.g., adrenal insufficiency such as Addisonian crisis or history of strong CYP3A4 inhibitors) and safety concerns (e.g., hyperkalemia, defined as serum potassium ≥5.5 mmol/L, as per the safety warnings for either finerenone or spironolactone). Eligibility criteria and baseline covariates were evaluated during the baseline period, defined as the one-year period prior to the index event. (Supplementary Table 2 and Supplementary Fig. 1).

Treatment strategies

Two treatment strategies were compared: initiation of finerenone or spironolactone at baseline (index event). Treatment initiation was defined as the first prescription of the respective medication (new-user design), following an intention-to-treat approach, with no adjustments for medication adherence, switches, or addition of other MRAs.

Prespecified outcomes

The primary outcomes were major adverse cardiovascular events (MACE), major adverse kidney events (MAKE), and all-cause mortality. MACE was defined as acute coronary syndromes, nonfatal stroke, hemorrhagic stroke, cardiac arrest, cardiogenic shock. To complement our primary definition, we additionally evaluated alternative MACE definitions based on narrower myocardial infarction criteria. MAKE was defined as progression to end-stage kidney disease (ESKD) or initiation of dialysis. The secondary outcome was hyperkalemia, assessed at thresholds of ≥5.5 mEq/L. Each patient was followed from the index event until the occurrence of an outcome of interest, loss to follow-up, death, administrative censoring (March 14, 2025), or a maximum follow-up period of 1.5 years, whichever occurred first (Supplementary Table 3).

Covariates

The predefined covariates, selected based on clinical knowledge and previous evidence, were measured within 1 year before the index event to balance treatment group differences. These included sociodemographic factors—age, race, sex, and socioeconomic status—as documented in the electronic health record; laboratory and vital sign measurements (glycated hemoglobin, eGFR, blood pressure, total cholesterol, low-density lipoprotein cholesterol, body mass index, and potassium); medications (insulin, metformin, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, renin-angiotensin system (RAS) inhibitors, β-blockers, calcium channel blockers, aspirin, anticoagulants, and hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors); comorbidities (ischemic heart disease, heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, atrial fibrillation and flutter, acute kidney injury, anemia, chronic obstructive pulmonary disease, liver disease, systemic connective tissue disorders, neoplasms, hyperuricemia, sleep apnea, depressive episodes, and anxiety disorders); diabetic complications (ophthalmic, neurologic, and circulatory); and lifestyle factors (nicotine dependence and alcohol-related disorders) (Supplementary Table 4).

Statistical analysis

To minimize confounding and emulate the randomization process, one-to-one propensity score matching (PSM) was performed using logistic regression with greedy nearest-neighbor matching and a caliper width of 0.1 pooled standardized differences[42]. Adequate balance between the matched groups was considered achieved when the standardized difference was less than 0.1, indicating minimal differences[48]. To address missing laboratory data (e.g., BMI, HbA1c, SBP, lipids, and UPCR), we included a distinct "no measurement" category for each variable in the propensity score model.

For the primary analysis, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models under an intention-to-treat framework. Cumulative incidence curves were generated using the Kaplan-Meier method, and differences were evaluated with the log-rank test. Absolute risk reduction (ARR) was calculated as the difference in event rates between groups, and number needed to treat (NNT) was derived as its reciprocal (NNT = 1/ARR). Confidence intervals for ARR and NNT were estimated using standard binomial methods. The incidence of hyperkalemia was assessed using odds ratios (ORs) with corresponding p values, which were derived from the chi-square test. To assess robustness to unmeasured confounding, we calculated E-values, with higher values indicating greater resistance to bias[49].

Predefined subgroup analyses were conducted in separate PSM cohorts stratified by clinically relevant baseline characteristics, including age, sex, glycated hemoglobin level, baseline eGFR, proteinuria, heart failure, and use of SGLT2 inhibitors and RAS inhibitors, and enrollment year, to examine potential effect modification. To assess treatment persistence, we calculated the proportion of patients with ongoing prescriptions at 6 and 12 months after initiation. As a sensitivity analysis, we performed landmark analyses at these timepoints, including only patients who were event-free and remained on treatment to examine the associations with subsequent outcomes. Additional analyses included conducting analyses before propensity score matching (PSM), excluding events within 30 days of treatment initiation to reduce misclassification bias, and limiting dose-specific analyses to participants with recorded drug doses. To minimize bias from treatment switching, patients who transitioned to the alternative medication class were excluded. We also restricted analyses to patients with complete laboratory data to assess the impact of missingness. A negative control outcome analysis was performed by examining the association between treatments and overall cancer incidence, for which no association was expected[50–53]. To avoid bias associated with the interpretation of composite endpoints, we further conducted specificity analyses on the individual components of the outcomes of interest.

All analyses were conducted using the TriNetX platform (TriNetX LLC, Cambridge, MA, USA) and R software (version 4.4.1; The R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value < 0.05 was considered statistically significant. Data were collected and analyzed from March 14, 2025, to April 30, 2025.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The aggregate-level data used in this study were obtained from the TriNetX platform. Due to TriNetX data sharing policies, individual-level data are not accessible to the authors. Requests for access to the datasets must include a description of the intended use and will be reviewed within 2 weeks. Upon approval, data access will be provided within 4 weeks, subject to institutional and data protection regulations. For data access inquiries, please contact the corresponding author, Vin-Cent Wu (q91421028@ntu.edu.tw). Source data are provided with this paper. High-resolution figures for this study, including cohort construction, outcome curves, and subgroup analyses, are publicly available at Figshare (https://doi.org/10.6084/m9.figshare.29487947.v1). Source data are provided with this paper.

Code availability

This study was conducted using the TriNetX Analytics Platform, a commercial, cloud-based real-world data research environment. All analyses were performed using the platform's built-in tools and interface. As TriNetX is a proprietary, closed-source system, the underlying codebase cannot be publicly shared. However, researchers with institutional access to TriNetX can replicate the analyses by following the detailed methodology described in the manuscript and supplementary materials.

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Author contributions

C.-A. Wang and V.-C. Wu had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C.-A. Wang, H.-W. Lai, and V.-C. Wu contributed to the concept and design of the study. C.-A. Wang and V.-C. Wu were involved in the acquisition, analysis, and interpretation of the data. C.-A. Wang drafted the manuscript, while C.-A. Wang, J.-Y. Chen, W.-J. Wang, and V.-C. Wu critically reviewed the manuscript for important intellectual content. C.-A. Wang and H.-W. Lai conducted the statistical analysis. L.-C. Lin and Y.-L. Chiu provided statistical consultation and contributed to the revision and interpretation of the results. J.-Y. Chen and C.-Y. Cheng provided administrative, technical, or material support. J.-Y. Chen, W.-J. Wang, C.-Y. Cheng, and V.-C. Wu supervised the study.

Competing interests

The authors declare no competing interests.

Additional information

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