

Cognitive and Renal Outcomes of Finerenone in Older Adults With Heart Failure With Preserved Ejection Fraction: A Real-World Cohort Study

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Abstract

Background

Heart failure with preserved ejection fraction (HFpEF) disproportionately affects older adults, in whom dementia and cognitive decline are frequent but underrecognized. Steroidal mineralocorticoid receptor antagonists (MRAs) have been linked to lower dementia risk. Whether this extends to finerenone is unknown.

Methods

This retrospective TriNetX cohort study identified adults aged ≥ 65 with a first HFpEF diagnosis (July 9, 2021–September 14, 2026). The primary outcome was six-month incidence of dementia or cognitive decline; the secondary was a composite adverse renal outcome.

Results

Each matched cohort included 1,660 patients. Dementia or cognitive decline occurred in 1% of the finerenone group versus 1.4% of controls (HR 0.9, 95%CI 0.46–1.60). The composite renal outcome was significantly lower with finerenone (11.1% vs 20.3%; HR 0.6, 95%CI 0.47–0.67).

Conclusion

In older adults with HFpEF, finerenone conferred renal benefit without a detectable short-term cognitive signal. Longer follow-up with standardized cognitive assessment is needed before excluding neuroprotection.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is predominantly a disease of older adults and accounts for 50% of all heart failure (HF) cases; however, disease-modifying therapy remains limited relative to reduced ejection fraction^{1,2}. The role of mineralocorticoid receptor antagonists (MRAs) in HFpEF, particularly steroidal agents, has yielded mixed results and remains an area of ongoing investigation¹. Finerenone, a nonsteroidal MRA with greater receptor selectivity than spironolactone or eplerenone, was first approved for chronic kidney disease (CKD) and type 2 diabetes (T2D) based on the FIDELIO-DKD and FIGARO-DKD trials, which demonstrated improved cardiovascular (CV) and renal outcomes^{1,3,4}. It has been shown to decrease the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks, and HF hospitalization^{1,3,4}. The subsequent FINEARTS-HF trial, conducted

in patients with HFpEF and heart failure with mildly reduced ejection fraction (HFmrEF), reported reduced HF hospitalization with no significant reduction in CV death or all-cause mortality ⁵.

Cognitive dysfunction and dementia are common, underrecognized comorbidities of HF, with increased prevalence independent of conventional risk factors for either condition ⁶. In the PARAGON-HF trial, HFpEF patients with worse cognitive function, as assessed by the Mini-Mental State Examination (MMSE), demonstrated poorer outcomes, including a higher risk of HF hospitalization or CV death ⁷. Beyond its association with adverse cardiovascular outcomes, cognitive impairment in older adults with HF compromises medication adherence, self-management of a complex treatment regimen, and functional independence, and increases caregiver burden ⁸. A prior TriNetX study of patients with heart failure with reduced ejection fraction (HFrEF) found spironolactone use associated with a lower 3-year risk of Alzheimer disease and dementia, although no difference was observed in the incidence of cognitive decline ⁹. Whether this benefit extends to finerenone is unclear, particularly given its reduced central nervous system penetration in comparison with steroidal MRAs, raising the question of whether any neuroprotective effect is centrally or peripherally mediated ¹. In addition, given finerenone's established renoprotective mechanism, specifically delaying CKD progression and reducing proteinuria in CKD and HFrEF patients, real-world characterization of its renal safety in patients with HFpEF is also warranted ^{1,10}. In addition, older adults with HFpEF frequently contend with polypharmacy and age-related declines in renal reserve, making the selection of agents with a favorable safety profile across multiple organ systems especially relevant to their care ¹¹.

Therefore, the aim of this retrospective study is to evaluate the six-month incidence of dementia and cognitive decline among older adults with HFpEF initiating finerenone compared with non-MRA controls, with a composite renal outcome as a secondary endpoint, given the clinical importance of both outcomes for functional independence and prescribing decisions in this age group.

Methods

Study Setting and Design

The current study used real-world de-identified data collected by accessing the TriNetX platform to construct a retrospective cohort design. The TriNetX Collaborative Research Network pools data from the electronic health records (EHR) of 118 healthcare organizations. The TriNetX platform collects data from various healthcare settings including inpatient admissions, emergency department (ED) visits, outpatient clinics, and electronic health encounters. Available data include demographics (age, sex, race, ethnicity), diagnoses (using the International Statistical Classification of Diseases and Related Health Problems [ICD] – 10 codes), procedures (Current Procedural Terminology [CPT] codes), laboratory results, medications prescribed, and clinical outcomes.

Study Population

The present study collected data on adult patients, older than 65-years, who had a first diagnosis of HFpEF (ICD-10: I50.3) on or after July 9, 2021, the date on which finerenone received approval from the US food and drug administration (FDA) for the management of CKD and T2D, and until September 14, 2026. The study population was divided into two study groups, an exposure group that initiated finerenone after a diagnosis in HFpEF; and a control group that did not use finerenone or other mineralocorticoid receptor antagonists during the study period. The starting date of data collection or index date was defined by initiation of finerenone therapy. Patients were followed until the occurrence of an outcome event, death, loss to follow-up, six-months (end of follow-up period), or Sep 14, 2026 (end of study period). Patients who had prescriptions for a mineralocorticoid receptor antagonist within six months from the index event were excluded. Patients with diagnosis of dementia or cognitive decline (as defined below) prior to the index event were also excluded. Other exclusion criteria included the presence of medical contraindications to finerenone as detailed in the drug packaging; namely, hyperkalemia (serum potassium level > 5.5 mmol/L), or renal insufficiency defined by estimated glomerular filtration rate (eGFR) < 25 ml/min/1.73m², advanced CKD/end-stage renal disease (ESRD) or dialysis dependence (ICD-10: N18.5, N18.6, Z99.2).

Outcomes

The primary outcome was the six-month incidence of dementia or cognitive decline (ICD-10: F01-F03, G30, G31, R41.81). A secondary outcome of a composite of kidney events including acute kidney injury, advanced CKD, ESRD, and need for dialysis (ICD-10: N17, N18.5, N18.6, Z99.2; CPT: 1012740) was also investigated.

Data collection and definitions

Possible confounding factors were adjusted for using one-to-one propensity score matching of clinically relevant covariates, as previously described. Covariates included in propensity score matching were sociodemographic factors (age at index, sex, race, ethnicity, socioeconomic status), comorbidities (obesity, T2D, hypertension, dyslipidemia, ischemic heart disease, atrial fibrillation or flutter, cerebrovascular disease, peripheral arterial disease, sleep apnea, CKD, thyroid disease), behavioral disorders (depression, tobacco smoking, alcohol use disorder), body mass index, systolic blood pressure, medications (sodium-glucose cotransporter-2 [SGLT2] inhibitors, glucagon-like 1 receptor agonists [GLP1-RA]), and laboratory values (eGFR, urine microalbumin-to-creatinine ratio [UACR]). All covariates were assessed beginning one year prior to the index event. Covariate definitions are provided in the Supplementary Materials.

Ethics approval and informed consent

All data used in the current study were collected from the TriNetX platform, which only contains de-identified patient data per the de-identification standard defined in Section § 164.514(a) of the HIPAA Privacy Rule. Thus, the study was exempt from institutional review board (IRB) approval and patient informed consent. The study was performed in line with the principles of the Declaration of Helsinki. All data analyses are secondary analyses of existing data. The study does not involve intervention or interaction with human subjects.

Statistical analysis

Covariates between the two study groups were compared at baseline. Categorical variables were reported as numbers and percentages and continuous variables as medians and interquartile ranges (IQR). Propensity score matching was performed by fitting logistic regression models that were adjusted for all covariates, using greedy nearest neighbor matching with calipers of width equal to 0.1 SD of the logit of the propensity score. To assess covariate balance between the two study groups after matching, standardized mean differences (SMD) were calculated, with $SMD < 0.01$ representing negligible covariate imbalance. The cumulative incidence of an outcome was calculated by dividing the number of patients in a group that had an occurrence of the outcome within the follow-up period by the number of patients in the group at the start of follow-up. Absolute risk difference (ARD) (the difference between the cumulative incidence of an outcome in the finerenone group and the cumulative incidence of that outcome in the control group). Kaplan Meier curves were constructed with intergroup differences assessed using log-rank tests. Cox proportional hazards analysis was performed to calculate hazard ratios (HR) with 95% confidence intervals (CI).

All analyses were conducted using the TriNetX platform (TriNetX LLC, Cambridge, MA, USA). A two-sided p value < 0.05 was considered statistically significant.

Results

Study population

During the study period (July 9, 2021 to September 14, 2026), 559,574 patients had a diagnosis of HFpEF and met the inclusion and exclusion criteria in the TriNetX platform. Of these, 1,665 patients were prescribed finerenone. After propensity score matching, two cohorts with 1,660 patients in each were formed (Fig. 1).

Baseline clinical characteristics

The baseline sociodemographic and clinical characteristics of the two study groups before and after propensity score matching are reported in Table 1.

In brief, prior to propensity score matching, the finerenone group had a greater comorbidity burden and worse eGFR and UACR compared to the control group. After propensity score matching, both groups had

similar characteristics with SMD < 0.1 for all covariates.

Clinical outcomes

The incidence, ARD and HR with 95% CIs for the primary and secondary outcomes are reported in Table 2. There was no significant difference in the risk of dementia or cognitive decline between the two study groups. The finerenone group had significantly lower incidence of kidney events compared to the control group.

Discussion

In this retrospective, propensity-matched, real-world cohort of patients with HFpEF, initiation of finerenone was not associated with a reduced six-month risk of dementia or cognitive decline compared with non-MRA controls. In contrast, finerenone was associated with a significantly lower incidence of the composite renal outcome, reaffirming its renoprotective profile in a population distinct from the CKD and T2D cohorts in which the drug was originally studied, a benefit relevant to older adults, for whom preserved renal function supports safer dosing and functional independence ^{1,3,4}.

The link between MRAs and cognitive function has been explored in previous studies, mostly spironolactone ⁹. In preclinical trials, spironolactone attenuated cognitive decline in mice with T2D ¹². The proposed benefit of MRAs stems from that mineralocorticosteroid receptors are expressed in the hippocampus and cerebral cortex, and their blockade has been proposed as the mechanism underlying this apparent cognitive protection, as the hippocampus is an area important for memory and affected in Alzheimer's ¹³. Clinically, the positive association between MRAs use and cognitive outcomes was reported as early as 2006, when antihypertensive medication use, and potassium-sparing diuretics in particular, was associated with a lower incidence of Alzheimer disease in an elderly cohort ¹⁴. In addition, a systematic review completed in 2025 across preclinical, healthy, psychiatric, and CV populations found that MRAs generally appeared to benefit cognitive function through systemic effects on cerebral blood flow and vascular inflammation rather than direct central receptor blockade alone, though spironolactone's effects varied depending on the population studied ¹³. A TriNetx analysis conducted in HFpEF patients using spironolactone demonstrated a lower three-year risk of Alzheimer disease and dementia, although no corresponding difference was seen in cognitive decline specifically ⁹.

Compared to spironolactone and eplerenone, finerenone bulkier, non-steroidal structure limits its blood-brain barrier penetration ¹. This distinction is clinically relevant, especially if the cognitive benefit observed with spironolactone is centrally mediated, finerenone's more limited CNS exposure would be expected to yield an attenuated effect, consistent with our findings ¹³. Alternatively, if the benefit is peripherally mediated, through improved cerebral perfusion, reduced vascular inflammation, or blood pressure effects, as proposed in the more recent systematic review, a six-month window may be too short to capture the effect that likely occurs over years, as it plausibly did in the previous three-year HFpEF spironolactone TriNetx analysis ^{9,13}. Distinguishing between these mechanisms is essential to

determine whether finerenone's apparent neutrality reflects a true absence of central effect or an effect that requires longer follow-up duration to become apparent. Moreover, age-related changes in blood-brain barrier permeability and renal drug clearance may further modify finerenone's central exposure in this older population, an interaction that has not been specifically characterized and that preclinical and pharmacokinetic studies in aging models could help clarify ¹⁵.

The reduced incidence of the composite renal outcome in the finerenone group is consistent with the mechanism established in FIDELIO-DKD and FIGARO-DKD, where finerenone slowed eGFR decline and reduced proteinuria in patients with CKD and T2D through its anti-fibrotic and anti-inflammatory effects on the kidney, that is independent of its CV actions ^{3,4}. Our results extended this renoprotective feature into the HFpEF population, a group in which renal dysfunction and cardiorenal syndrome are common and often bidirectionally aggravate outcomes. This renoprotective signal is particularly meaningful in older adults, in whom declining renal function accelerates frailty, complicates dosing of concomitant medications, and increases risk of hospitalization and loss of functional independence ¹⁶.

This study has several strengths, including its large, real-world, multi-institutional sample and rigorous propensity score matching. Limitations include the retrospective, non-randomized design, reliance on ICD-10 and CPT coding for outcome ascertainment rather than adjudicated clinical events or formal cognitive assessment, and a relatively short follow-up period to a slowly evolving outcome like dementia.

This real-world analysis of patients with HFpEF found that finerenone initiation was not associated with a diminished six-month risk of dementia or cognitive decline compared with non-MRA therapy, suggesting that the neuroprotective signal reported with steroidal MRAs such as spironolactone may not extend, at least in the short term, to this non-steroidal agent. By contrast, finerenone was associated with a significantly lower incidence of adverse renal events, reinforcing that the renal benefits of finerenone generalize across the cardiometabolic-renal continuum rather than being confined to the CKD/T2D population, a particularly meaningful finding for older adults, in whom preserving renal function helps guard against frailty, complications from polypharmacy, and loss of functional independence. These findings support finerenone's continued use for its cardiorenal benefits in HFpEF while tempering expectations of an early cognitive benefit. Longer-term studies incorporating standardized cognitive assessment, and ideally prospective or randomized data, are needed to determine whether a neuroprotective effect of finerenone emerges over a longer time horizon in this aging population.

References

1. Kintscher U, Edelmann F (2023) The non-steroidal mineralocorticoid receptor antagonist finerenone and heart failure with preserved ejection fraction. *Cardiovasc Diabetol* 22(1):162. 10.1186/s12933-023-01899-0
2. Upadhyia B, Kitzman DW (2020) Heart failure with preserved ejection fraction: New approaches to diagnosis and management. *Clin Cardiol* 43(2):145–155. 10.1002/clc.23321

3. Pitt B, Filippatos G, Agarwal R et al (2021) Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *N Engl J Med* 385(24):2252–2263. 10.1056/NEJMoa2110956
4. Bakris GL, Agarwal R, Anker SD et al (2020) Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med* 383(23):2219–2229. 10.1056/NEJMoa2025845
5. Solomon SD, McMurray JJV, Vaduganathan M et al (2024) Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med* 391(16):1475–1485. 10.1056/NEJMoa2407107
6. Witt LS, Rotter J, Stearns SC et al (2018) Heart Failure and Cognitive Impairment in the Atherosclerosis Risk in Communities (ARIC) Study. *J Gen Intern Med* 33(10):1721–1728. 10.1007/s11606-018-4556-x
7. Shen L, Dewan P, Ferreira JP et al (2024) Clinical Correlates and Prognostic Impact of Cognitive Dysfunction in Patients With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. *Circulation* 150(24):1913–1927. 10.1161/CIRCULATIONAHA.124.070553
8. Li M, Zhang J, Hu Y, Zhang Y (2025) Cognitive impairment in patients with heart failure: Physiopathology, clinical implications, and therapeutic considerations. *J Cardiol* 85(6):465–472. 10.1016/j.jjcc.2025.02.007
9. Pastena P, Skopicki H, Halterman M, Kalogeropoulos A (2024) Spironolactone Use And Neurocognitive Outcomes Among Patients With Heart Failure And Reduced Ejection Fraction. *J Card Fail* 30(1):258–259. 10.1016/j.cardfail.2023.10.337
10. Ramadan MM, Alajmi S, Aldouser J et al (2025) Pharmacology and Therapeutic Potential of Finerenone: A Novel Third-Generation Nonsteroidal Mineralocorticoid Receptor Antagonist. *Cureus* 17(7):e87706. 10.7759/cureus.87706
11. Dacquino GM, Galati G, Genovese L et al (2026) Cardiovascular risk management in the elderly: a dilemma in daily clinical practice. *Eur J Prev Cardiol* 33(Supplement3):iii13–iii25. 10.1093/eurjpc/zwag316
12. Sakata A, Mogi M, Iwanami J et al (2012) Improvement of cognitive impairment in female type 2 diabetes mellitus mice by spironolactone. *J Renin-Angiotensin-Aldosterone Syst JRAAS* 13(1):84–90. 10.1177/1470320311412810
13. Pastena P, Campagnoli G, Rahmani AR, Kalogeropoulos AP (2025) Mineralocorticoid Receptor Antagonists and Cognitive Outcomes in Cardiovascular Disease and Beyond: A Systematic Review. *J Pers Med* 15(2):57. 10.3390/jpm15020057
14. Khachaturian AS (2006) Antihypertensive Medication Use and Incident Alzheimer Disease: The Cache County Study. *Arch Neurol* 63(5):686. 10.1001/archneur.63.5.noc60013
15. Farrall AJ, Wardlaw JM (2009) Blood-brain barrier: ageing and microvascular disease—systematic review and meta-analysis. *Neurobiol Aging* 30(3):337–352. 10.1016/j.neurobiolaging.2007.07.015
16. Wilhelm-Leen ER, Hall YN, Tamura K, Chertow M (2009) Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med* 122(7):664–671e2. 10.1016/j.amjmed.2009.01.026

Tables

Table 1. Baseline characteristics of patients using finerenone and controls before and after matching.

Characteristic	Patients prior to matching			Patients after matching		
	Finerenone	Control	SMD	Finerenone	Control	SMD
	N= 1,764	N= 546,873		N= 1,758	N= 1,758	
Age at Index, median (IQR)	75 [10]	75 [12]	0.053	75 [10]	76 [11]	0.032
Female sex, n (%)	834 (47.3)	291,281 (53.3)	0.12	829 (47.2)	820 (46.6)	0.01
Ethnicity, n (%)						
Hispanic or Latino	116 (6.6)	20,266 (3.7)	0.13	116 (6.6)	142 (8.1)	0.057
Not Hispanic or Latino	1,463 (82.9)	438,470 (80.2)	0.071	1,457 (82.9)	1,446 (82.3)	0.016
Race, n (%)						
White	1,136 (64.4)	428,602 (78.4)	0.313	1,136 (64.6)	1,130 (64.3)	0.007
Black or African American	232 (13.2)	65,486 (12)	0.036	232 (13.2)	244 (13.9)	0.02
Asian	194 (11)	14,130 (2.6)	0.339	189 (10.8)	190 (10.8)	0.002
Persons with potential health hazards related to socioeconomic circumstances	72 (4.1)	13,330 (2.4)	0.093	71 (4)	65 (3.7)	0.018
Body Mass Index, median [IQR]	31 [10]	30 [10]	0.093	31 [10.3]	32 [10.4]	0.017
Systolic blood pressure, median [IQR]	129 [24]	130 [24]	0.027	129 [24]	129 [25]	0.028
Comorbidities, n (%)						
Obesity	669 (37.9)	113,504 (20.8)	0.384	666 (37.9)	655 (37.3)	0.013
Hypertension	1,362 (77.2)	320,722 (58.6)	0.406	1,356 (77.1)	1,388 (79)	0.044
Dyslipidemia	1,338 (75.9)	284,526 (52)	0.512	1,332 (75.8)	1,343 (76.4)	0.015
Type 2 diabetes	1,143 (64.8)	154,768 (28.3)	0.786	1,138 (64.7)	1,146 (65.2)	0.01
Cerebrovascular disease	286 (16.2)	64,801 (11.8)	0.126	284 (16.2)	293 (16.7)	0.014

Ischemic heart disease	1,016 (57.6)	191,128 (34.9)	0.466	1,011 (57.5)	1,037 (59)	0.03
Atrial fibrillation and flutter	723 (41)	155,512 (28.4)	0.266	718 (40.8)	752 (42.8)	0.039
Chronic kidney disease	1,008 (57.1)	100,571 (18.4)	0.872	1,002 (57)	1,047 (59.6)	0.052
Thyroid disease	367 (20.8)	92,312 (16.9)	0.1	364 (20.7)	391 (22.2)	0.037
Peripheral arterial disease	540 (30.6)	108,984 (19.9)	0.248	536 (30.5)	534 (30.4)	0.002
Depression	79 (4.5)	20,355 (3.7)	0.038	79 (4.5)	83 (4.7)	0.011
Lifestyle factors, n (%)						
Nicotine dependence	139 (7.9)	46,259 (8.5)	0.021	139 (7.9)	140 (8)	0.002
Alcohol related disorders	33 (1.9)	12,670 (2.3)	0.031	33 (1.9)	27 (1.5)	0.026
Medications, n (%)						
SGLT2 inhibitors	786 (44.6)	28,476 (5.2)	1.022	780 (44.4)	775 (44.1)	0.006
GLP1-RA	304 (17.2)	19,033 (3.5)	0.463	301 (17.1)	319 (18.1)	0.027
Tirzepatide	142 (8.1)	4,550 (0.8)	0.356	140 (8)	118 (6.7)	0.048
Laboratory values, median [IQR]						
eGFR, mL/min/1.73 m ²	48 [25.5]	65.2 [31.4]	0.699	48.2 [25.5]	49.2 [25.2]	0.031
UACR, mg/g	193 [607.2]	33 [100.7]	0.208	191.7 [605.5]	102 [376.7]	0.055

Table 2. Incidence of dementia and kidney events in patients using finerenone and matched controls.

Outcome	No. of patients with outcome	Cumulative incidence (%)	ARD (95% CI, %)	HR (95% CI)
Dementia or cognitive decline				
Finerenone	17	1	-0.4 (-1.11 to 0.37)	0.9 (0.46–1.60)
Control	23	1.4	0 (Ref)	1 (Ref)
Kidney events				
Finerenone	195	11.1	-9.2 (-11.54 to -6.77)	0.6 (0.47–0.67)
Control	356	20.3	0 (Ref)	1 (Ref)

Figures

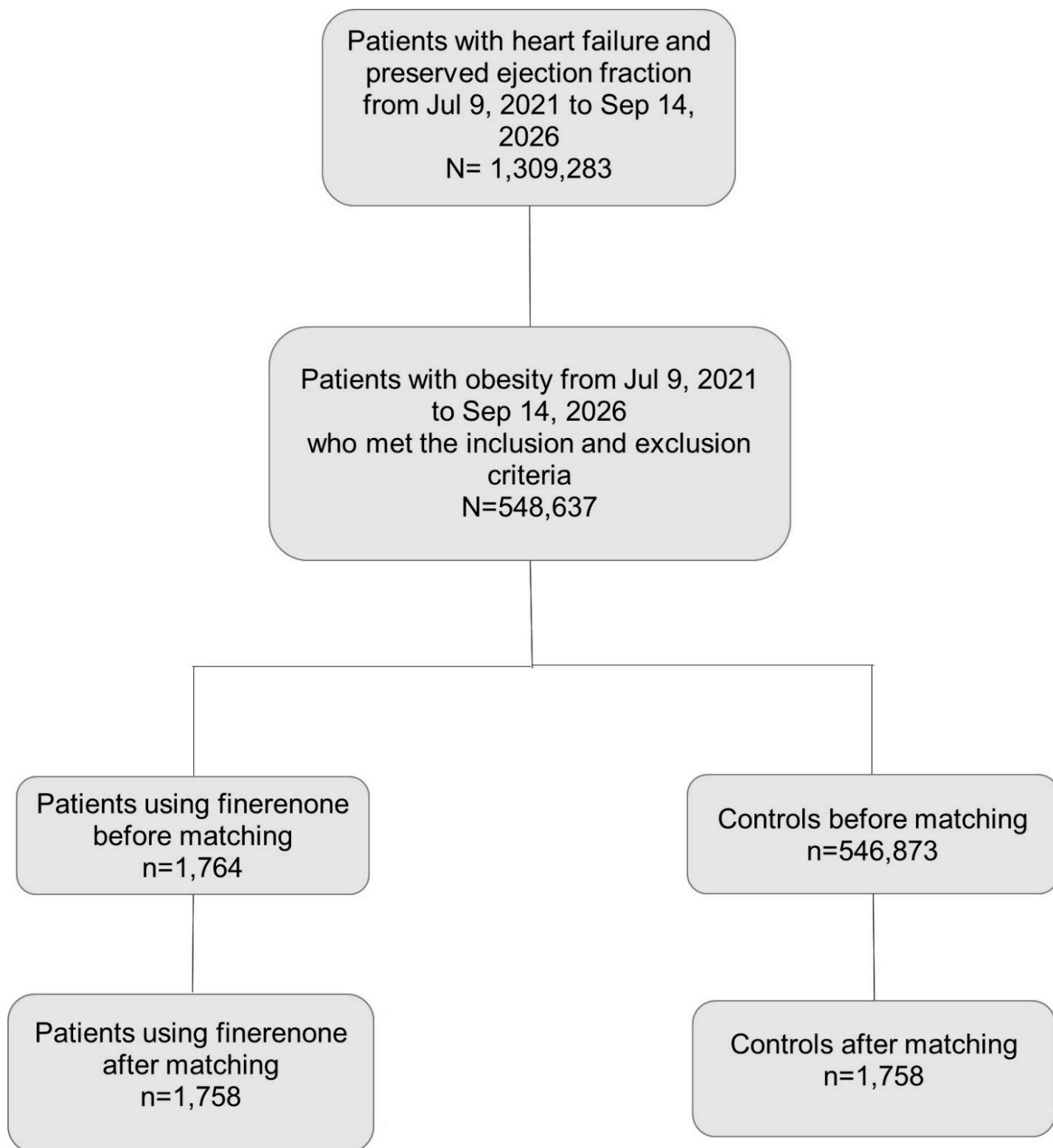


Figure 1

Flowchart for study population

Supplementary Files

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