ORIGINAL ARTICLE

CONTENTS

Effects of angiotensin converting enzyme inhibitors *versus* angiotensin receptor blockers on cognitive decline: A retrospective real-world database study

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ABSTRACT

Aim: To compare 5-year cognitive outcomes in patients with HFrEF who receive angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Materials and Methods: Retrospective cohort study of: 1) 135,873 adults with HFrEF (International Classification of Diseases-10th Revision-Clinical Modification [ICD-10-CM] codes: I50.2 or I50.4) started on ACEI between Aug 1, 2019 and Aug 1, 2024; and 2) 135,873 propensity matched patients receiving ARBs during that time. Data were obtained from the TriNetX Research Network, encompassing 80 health care organizations in the United States. The primary endpoint was the composite of cognitive decline (ICD-10-CM: R41.8), dementia (ICD-10-CM: F01-F03), and Alzheimer's disease (ICD-10- CM: G30).

Results: At 5 years,17,679 patients on ACEI met the primary endpoint vs 16,345 patients on ARBs (5-year incidence: 30.71% *vs* 28.54%; HR: 1.153; 95% CI: 129-1.178; P < 0.001), with consistently higher rates of cognitive decline (24.94% *vs* 22.81%; HR: 1.146; 95% CI: 1.119-1.174; P < 0.001), dementia (15.63% *vs* 13.71%; HR:1.204; 95% CI: 1.168-1.241; P < 0.001), and Alzheimer's disease (4.15% *vs* 3.51%; HR: 1.202; 95% CI: 1.131-1.277; P < 0.001) in the ACEI cohort.

Conclusions: ACEI was associated with higher 5-year rates of neurocognitive disorders when compared to ARBs in patients with HFrEF.

KEY WORDS: ACEIs, ARBs, HFrEF, cognitive decline, dementia, neurocognitive disorders

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LIST OF ABBREVIATIONS

- ACEI – Angiotensin-Converting Enzyme Inhibitor
- ACEIs – Angiotensin-Converting Enzyme Inhibitors
- ARB – Angiotensin Receptor Blocker
- ARBs – Angiotensin Receptor Blockers
- AT2R – Angiotensin II Type 2 Receptor
- CI – Confidence Interval
- CogState – Cognitive State Test
- CPT – Current Procedural Terminology
- CV – Cardiovascular
- GDMT – Guideline-Directed Medical Therapy
- HF – Heart Failure
- HFmrEF – Heart Failure with Mildly Reduced Ejection Fraction
- HFpEF – Heart Failure with Preserved Ejection Fraction
- HFrEF – Heart Failure with Reduced Ejection Fraction
- HR – Hazard Ratio
- ICD-10-CM – International Classification of Diseases, 10th Revision, Clinical Modification
- IRB – Institutional Review Board
- LVEF – Left Ventricular Ejection Fraction
- LOINC – Logical Observation Identifiers Names and Codes
- MCI – Mild Cognitive Impairment
- NF-κB – Nuclear Factor Kappa B
- PP2A – Protein Phosphatase 2A
- RCT – Randomized Controlled Trial
- RAS – Renin–Angiotensin System
- RASB – Renin–Angiotensin System Blockade
- RECORD – Reporting of Studies Conducted Using Observational Routinely Collected Health Data
- RxNorm – Prescription Normalized Nomenclature
- STAT3 – Signal Transducer and Activator of Transcription 3

INTRODUCTION

Heart failure is a common diagnosis in routine clinical practice, where the symptoms result from a structural or functional heart disorder that reduces the ventricular

function in filling with or ejecting blood. It is classified on the basis of left ventricular ejection fraction (LVEF) into heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and heart failure with mildly reduced ejection fraction (HFmrEF). Among all these groups, HFrEF has the strongest evidence base supporting medical therapy, since the majority of clinical trials have enrolled predominantly reduced ejection fraction patients.

Cognitive impairment is a common and clinically important complication of heart failure with reduced ejection fraction (HFrEF). In addition to mild cognitive impairment, HFrEF patients also have an increased incidence of dementia, including Alzheimer's disease, compared with the general population; however, HFrEF is more strongly related to vascular and mixed dementias than to pure Alzheimer's disease. The mechanisms are multifactorial, with reduced cardiac output as a central contributor, leading to cerebral hypoperfusion, neuroinflammation, oxidative stress, and progressive neurodegeneration [1].

The renin–angiotensin system (RAS) plays a critical role in the development of heart failure, as well as in cognitive outcomes. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are key therapies in patients with HFrEF, improving survival and reducing hospitalizations [2].

Beyond cardiovascular benefits, observational studies and meta-analyses suggest that both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are associated with a lower incidence of dementia compared with no RAS inhibition [3], [4]. However, Some studies concluded that ARBs may offer better protection, but this is not well established in the medical literature, and most available evidence comes from studies evaluating their use as antihypertensive agents in patients with hypertension rather than in heart failure patients [5].

Given the high burden of neurocognitive decline in HFrEF and the widespread use of ACEIs and ARBs as part of the Guideline Directed Medical Therapy (GDMT), understanding their comparative effects on cognition is highly relevant to clinical practice. This study therefore aims to compare the incidence of new-onset neurocognitive disorders in patients with HFrEF treated with ACEIs versus ARBs using a large, multicenter, real-world cohort.

AIM

The aim of this study is to fill the current knowledge gap by comparing the incidence of neurocognitive disorders in patients with HFrEF who receive angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

MATERIALS AND METHODS

DATA SOURCE AND STUDY DESIGN

This research was a retrospective, observational, propensity score matched cohort study using data from the TriNetX database. TriNetX is a global electronic health records network that provides access to anonymized patient data. In this study, data were obtained from 147 healthcare organizations in the United States, with 80 providers supplying patient data. The variables obtained from TriNetX included demographics, diagnoses, procedures, laboratory results, and medications, using standardized coding systems: ICD-10-CM and CPT for diagnoses and procedures, LOINC for laboratory values, and RxNorm for medications. A detailed list of codes and subcodes is available in the Supplemental Appendix. TriNetX, LLC holds a waiver from the Western IRB and adheres to HIPAA regulations, as only de-identified data are utilized. Data from the final search, conducted on August 10, 2025, were included in this analysis. This study was designed and reported in accordance with the RECORD guidelines to maintain quality and transparency.

STUDY POPULATION

From 80 healthcare organizations participating in TriNetX, we identified adult patients (age >18 years) with a diagnosis of HFrEF (ICD-10- CM codes I50.2 or I50.4) between Aug 1, 2019 and Aug 1, 2024, who was started on ACEI at the index visit but did not receive subsequent prescription of sacubitril/valsartan or ARB, those patients formed the parent ACEI cohort.

Patients who share the same baseline characteristics, diagnosis and healthcare encounter criteria but were treated with ARBs only across the same period of inception make up the parent ARBs cohort.

MAIN EXPOSURES

Drugs in TriNetX are recorded at the ingredient level, coded to RxNorm, and organized by Veterans Administration National Drug File therapeutic classes. For the purposes of this research, exposures of interest included ACE inhibitors (CV800), angiotensin receptor blockers (ARBs; CV805), and combination therapies for hypertension (CV400), including sacubitril as an ingredient (RxNorm code: 1656328). Supplementary Appendix contains further subcodes.

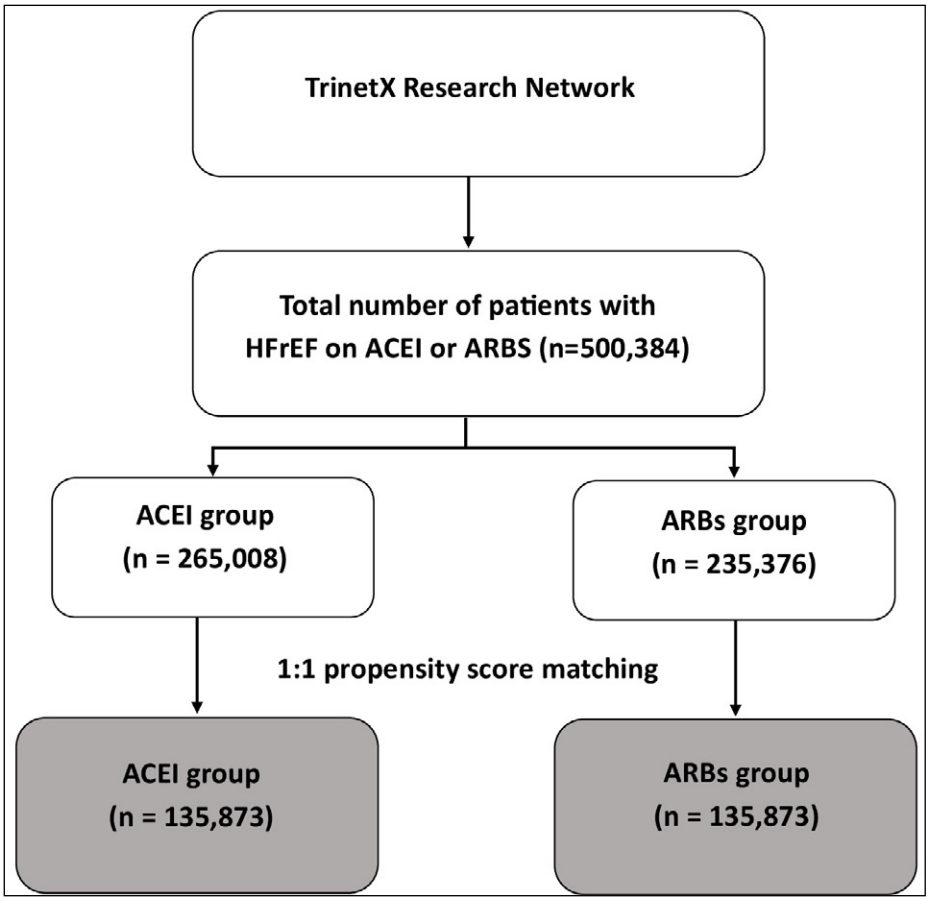

Fig. 1. Flow diagram of patient selection and cohort derivation following propensity score matching.
Source: Own materials

OUTCOMES

The primary outcome was the incidence of new neurocognitive diagnoses identified through ICD-10-CM codes, defined as the composite of cognitive decline (ICD-10-CM: R41.8), dementia (ICD-10- CM: F01-F03), and Alzheimer's disease (ICD-10-CM: G30), and these were assessed at 5 years. A 5-year follow-up window was selected to minimize censoring and maximize the follow-up. Each of the primary endpoint components were evaluated separately as a secondary endpoint (cognitive decline, dementia, and Alzheimer's disease). In subgroup analyses, we also investigated dementia subtypes, which included vascular dementia (F01), dementia in other diseases classified elsewhere (F02), and unspecified dementia (F03).

STATISTICAL ANALYSIS

Statistical analysis was performed using the TriNetX web-based platform. Propensity score matching was performed at a 1:1 ratio to create balanced cohorts, including the following characteristics: demographics, comorbidities, medications and laboratory results. Propensity scores were computed using logistic regression based on the predicted probability of a patient belonging to a certain cohort.

For each case in the smaller cohort, the system finds a match in the larger cohort using the greedy nearest neighbor approach with a caliper of 0.1 pooled standard deviations. The order of records is randomized to eliminate bias using a fixed seed during matching, allowing for reproducibility. Outcomes of interest were only compared within matched cohorts and subgroups of cohorts.

The TriNetX platform employs Kaplan–Meier survival analysis in order to estimate the incidence of the outcome of interest and compares the distribution of the eventfree curves with the log-rank test. Patients with any occurrence of any outcome of interest before the inception window were excluded from outcome analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox proportional hazards regression using the R survival package (v3.2-3). The proportional hazards assumption was tested with scaled Schoenfeld residuals. The two-tailed p-value ≤0.05 was considered statistically significant.

ETHICS APPROVAL

This study was conducted using de-identified data from the TriNetX research network. In accordance with U.S.

Table 1. Baseline characteristics of patients in ACEI and ARBs groups before and after propensity score matching (PSM)

	Before PSM			After PSM		
	Before Matching (ACEI group, n=170,555)	**Before Matching (ARBs group, n=309,793)**	**Standardized Difference**	**After Matching (ACEI group, n=138,051)**	**After Matching (ARBs group, n=138,051)**	**Standardized Difference**
Demographics						
Current Age (Mean ± SD)	72.4 ± 13.5	73.7 ± 13.1	0.103	72.1 ± 14.0	72.2 ± 13.2	0.006
Age at Index (Mean ± SD)	68.2 ± 13.9	70.0 ± 13.3	0.131	68.6±14.4	68.6±13.4	0.001
Female (%)	93,860 (35.4%)	101,666 (43.2%)	0.160	53,126(39.1%)	52,852(38.9%)	0.004
Male (%)	162,734 (61.4%)	126,770 (53.9%)	0.153	78,788(58.0%)	78,983(58.1%)	0.003
White (%)	186,005(70.2%)	146,293 (62.2%)	0.170	87,597(64.5%)	88,369 (65.0%)	0.012
Black or African American(%)	40,976(15.5%)	44,844(19.1%)	0.095	24,277(17.9%)	23,597(17.4%)	0.013
Asian(%)	5,868(2.2%)	11,249(4.8%)	0.140	4,413(3.2%)	4,462(3.3%)	0.002
Comorbid conditions						
Hypertension	186,648(70.4%)	169,194(71.9%)	0.032	83,887 (61.7%)	84,699 (62.3%)	0.012
Dyslipidemia	165,728(62.5%)	150,648(64%)	0.030	75,125(55.3%)	75,857 (55.8%)	0.011
Mental, Behavioral and Neurodevelopmental disorders	133,563(50.4%)	107,693(45.8%)	0.093	58,393(43.0%)	59,602(43.9%)	0.018
Ischemic heart diseases	142,957(53.9%)	124,370(52.8%)	0.022	65,972(48.6%)	66,853(49.2%)	0.013
Atrial fibrillation and flutter	85,889(32.4%)	77,430(32.9%)	0.010	40,883(30.1%)	41,457 (30.5%)	0.009
Diabetes mellitus	107,133(40.4%)	97,107(41.3%)	0.017	49,300(36.3%)	49,641(36.5%)	0.005
Pulmonary heart disease and diseases of pulmonary circulation	44,149(16.7%)	40,819(17.3%)	0.018	20,792(15.3%)	21,100(15.5%)	0.006
Diseases of the respiratory system	159,650(60.2%)	143,580(61%)	0.015	73,999(54.5%%)	74,735(55%)	0.011
Cerebrovascular diseases	56,291(21.2%)	50,018(21.3%)	0.938	25,235(18.6%)	25,598(18.8%)	0.007
Nicotine dependence	60,161(22.7%)	38,795 (16.5%)	0.157	23,975(17.6%)	24,515(18%)	0.010
Medication use						
Aspirin	143,585(54.2%)	122,650(52.1%)	0.042	59,460(43.8%)	60,651(44.6%)	0.018
Beta-blockers	173,250(65.4%)	152,470(64.8%)	0.013	74,208(54.6%)	75,264(55.4%)	0.016
Calcium-channel blockers	104,332(39.4%)	105,359(44.8%)	0.109	47,351(34.8%)	47,694(35.1%)	0.005
Diuretics	155,398(58.6%)	143,438(60.9%)	0.047	66,681(49.1%)	67,682(49.8%)	0.016
Antilipemic agents	157,665(59.5%)	137,695(58.5%)	0.020	65,012(47.8%)	66,257(48.8%)	0.018
Previous use of ACEI	131,785(49.7%)	48,142(20.5%)	0.644	27,393(20.2%)	28,713(21.1%)	0.024
Previous use of ARBs	15,173(5.7%)	96,003(40.8%)	0.912	15,173(11.2%)	16,673(12.3%)	0.034
Vitamins	100,836(38.1%)	93,419(39.7%)	0.034	42,963(31.6%)	43,735(32.2%)	0.012
Herbs and alternative therapy	68,584(25.9%)	65,195(27.7%)	0.041	32,552(24.0%)	32,755(24.1%)	0.003
Laboratory						
NT-proBNP, pg/mL	4332.5 ± 8401.5	4588.1 ± 8914.8	0.030	5121.0 ± 9264.4	5031.2 ± 9265.6	0.010
Total cholesterol, md/dL	157.2 ± 47.5	158.9 ± 46.6	0.038	158.5 ± 49.1	159.3 ± 48.0	0.017
Hemoglobin A1c, %	6.7 ± 1.9	6.7 ± 1.8	0.047	6.7 ± 1.9	6.6 ± 1.8	0.033
Iron, mcg/dL	61.0 ±42.5	61.1 ± 41.1	0.001	58.9 ± 42.4	60.4 ± 42.2	0.035
Ferritin, ng/mL	340.6 ± 1307.1	334.6 ± 1028.5	0.005	399.5 ± 1663.7	368.6 ±1197.8	0.021
Blood urea nitrogen, mg/dL	22.1 ± 13.1	23.6 ±14.5	0.104	22.7 ± 13.9	23.3 ±14.6	0.043
Creatinine, mg/dL	1.4 ±3.8	1.5 ± 3.5	0.043	1.5 ±4.9	1.5 ±3.4	<0.001

Source: Own materials

federal regulations, studies using only de-identified data are not considered human subjects research and are exempt from institutional review board (IRB) approval. TriNetX, LLC has received a waiver from the Western IRB and complies with the Health Insurance Portability and Accountability Act (HIPAA), with

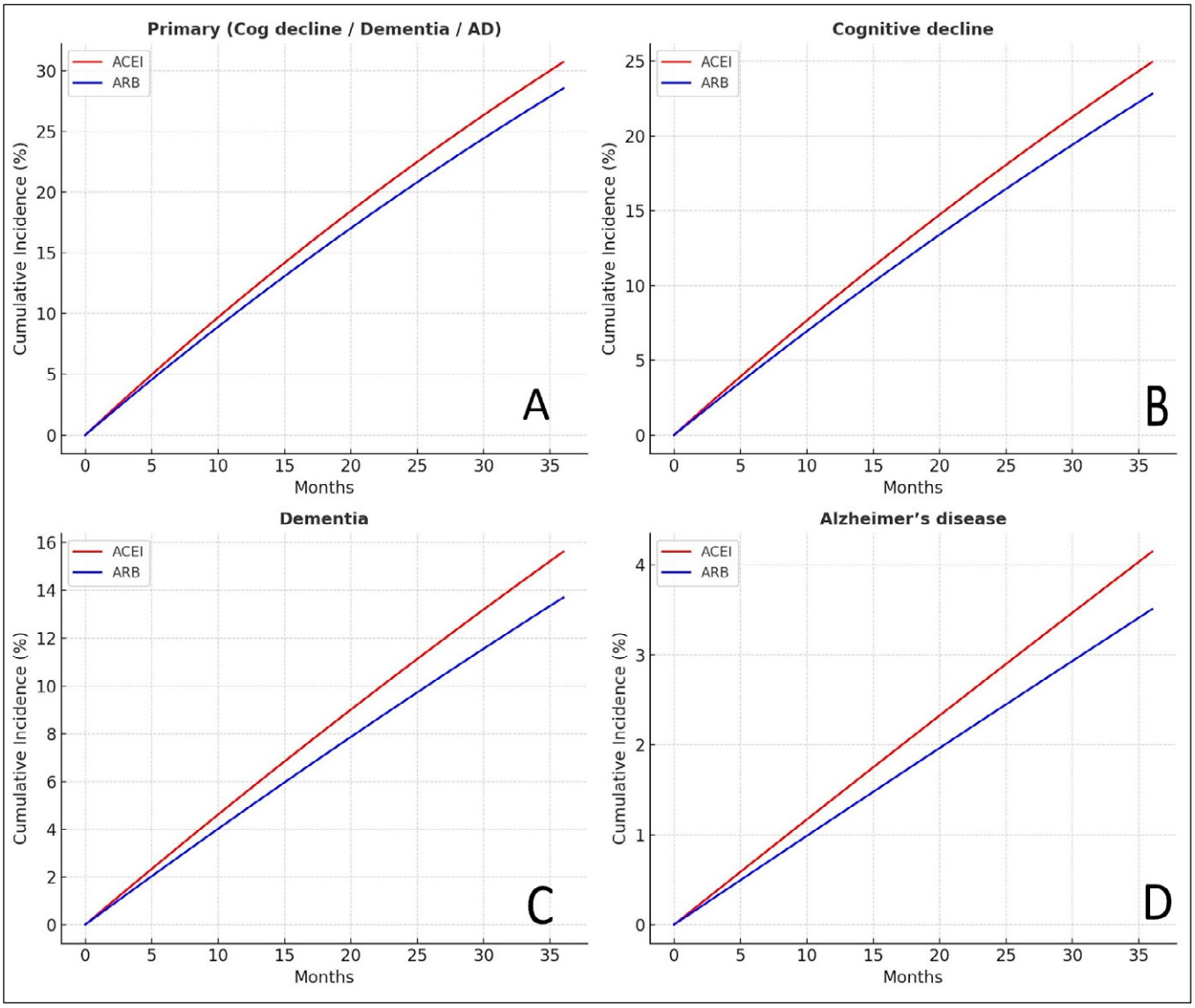

Fig. 2. Cumulative incidence of the primary and secondary outcomes: (A) the primary endpoint (cognitive decline, dementia, or Alzheimer's disease), (B) cognitive decline; (C) dementia; and (D) Alzheimer's disease, among patients with heart failure and reduced ejection fraction who started receiving ACEI *vs* propensity score-matched patients receiving ARBs with an index encounter during the same timeframe. Patients were captured from the TriNetX database

Source: Own materials

de-identification confirmed through a qualified expert determination as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule.

RESULTS

BASELINE CHARACTERISTICS

Using TriNetx database we select 265,008 adults with HFrEF (I50.2 or I50.4) who started receiving ACEI between 2019 and 2024 without any subsequent exposure to ARB and 235,376 patients who received ARBs exclusively during the same period. After propensity score matching for the characteristics described in the methods, the matched cohorts comprised 135,873 patients, each summarizes the characteristics of the parent cohorts before and after the propensity score matching (Fig. 1, Table 1). Patients in the ACEI matched cohort were 68.6 ± 14.4 years of age; 58.0% were men; 64.5% were White, 17.9% Black, and 3.2% Asian; and 20.2% were previously on ACEI and 11.2% were on ARBs. The most prevalent comorbidities were hypertension (61.7%), dyslipidemia (55.3%), and respiratory disorders (54.5%), followed by ischemic heart disease (48.6%), mental and behavioral disorders (43.0%), diabetes mellitus (36.3%), and atrial fibrillation (30.1%). All characteristics of the matched ACEI cohort demonstrated standardized mean differences <0.1 *vs* the ARBs cohort.

Table 2. Primary and secondary clinical outcomes: ACEI *vs*. ARBs in HFrEF patients

	ACEI (n =135,873)		ARBs (n =135,873)			
	Events	3-y K-M Estimate	Events	3-y K-M Estimate	HR (95% CI)	P Value
Primary endpoint	17,679	30.71%	16,345	28.54%	1.153 (1.129–1.178)	<0.001
Cognitive decline	13,793	24.94%	12,750	22.81%	1.146 (1.119–1.174)	<0.001
Dementia	9,154	15.63%	8,001	13.71%	1.204 (1.168–1.241)	<0.001
Alzheimer's disease	2,269	4.15%	1,972	3.51%	1.202 (1.131–1.277)	<0.001

Source: Own materials

Table 3. Dementia subtypes: ACEI vs. ARBs in HFrEF patients

	ACEI (n =135,873)		ARBs (n =135,873)			
	Events	3-y K-M Estimate	Events	3-y K-M Estimate	HR (95% CI)	P Value
Vascular dementia	2,152	3.86%	1,925	3.41%	1.167 (1.097–1.241)	<0.001
Unspecified dementia	8,098	14.1%	6,878	12.0%	1.238 (1.199–1.278)	<0.001
Dementia in other diseases	3,193	5.56%	2,794	4.93%	1.202 (1.131–1.277)	<0.001

Source: Own materials

INCIDENCE OF NEUROCOGNITIVE DIAGNOSES

At 5 years, the primary endpoint (incident cognitive decline, dementia, or Alzheimer's disease) was met by 17,679 patients in the ACEI vs 16,345 patients in the ARBs matched cohorts. The corresponding Kaplan-Meier cumulative 5-year incidence was 30.71% *vs* 28.54%, with a HR of 1.153 (95% CI: 1.129-1.178; P < 0.001) (Fig. 2A and Table 2). The 5-year Kaplan-Meier incidence of the secondary endpoints was consistently higher in the ACEI cohort; 24.94% vs 22.81% for cognitive decline (HR: 1.146; 95% CI: 1.119-1.174; P < 0.001), 15.63% vs 13.71% for dementia (HR: 1.204; 95% CI: 1.168-1.241; P < 0.001), and 4.15% vs 3.51% for Alzheimer's disease (HR: 1.202; 95% CI: 1.131-1.277; P < 0.001), (Fig. 2B-D, Fig. 3 and Table 2). In an exploratory analysis, we examined the incidence of subtypes of dementia (vascular dementia [F01], dementia in other diseases [F02], and unspecified dementia [F03]). The results were consistent across dementia subtypes (Table 3). The 5-year Kaplan-Meier incidence of the dementia subtypes was consistently higher in the ACEI cohort; 3.86% vs 3.41%% for vascular dementia (HR: 1.167; 95% CI: 1.097-1.241; P < 0.001), 14.1% vs 12.0% for unspecified dementia (HR: 1.238; 95% CI: 1.199-1.278; P < 0.001), and 5.56% vs 4.93% for Dementia in other diseases (HR: 1.195; 95% CI: 1.135-1.257; P < 0.001) (Table 3).

DISCUSSION

ACEIs and ARBs are well-established components of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) and are also widely prescribed as first-line agents for hypertension. Both drug classes have been associated with delayed progression of cognitive decline and a reduced risk of incident dementia; this effect is largely linked to blood pressure control [3]. In addition to this effect, recent research papers suggest that ACEIs and ARBs may also have neuroprotective benefits independent of their effect on blood pressure [3,4], with ARBs generally showed better outcomes compared with ACEIs [6].

Current evidence suggests that both ACE inhibitors and angiotensin receptor blockers may be associated with improved or preserved cognition in patients with heart failure, but ARBs may offer greater benefit in reducing progression to dementia, and definitive conclusions are limited by the quality and heterogeneity of available studies [7] .

In this large, multicenter, propensity-matched cohort study of patients with HFrEF, treatment with ARBs was associated with a significantly lower 5-year incidence of new-onset neurocognitive disorders compared with ACEIs. This protective association was consistent across the composite outcome of cognitive decline, dementia, and Alzheimer's disease.

These findings are in line with a recent randomized controlled trial by Hajjar et al. (2025) [8]. This RCT showed that the use of candesartan resulted in better neurocognitive outcome compared with lisinopril in older adults with MCI after 1-year of treatment. This effect is likely independent of the blood pressure lowering effect of candesartan.

The exact mechanism of this effect is not well established, but experimental data [9] attribute the protective effect of ARBs to the increased activation of the angiotensin II type 2 receptor (AT2R), leading to protein phosphatase 2A (PP2A) activation, stabilization of IκBα, and suppression of NF-κB and STAT3 inflammatory signaling. Thereby reducing Neuroinflammation, which is usually viewed as the preceding event in neurodegeneration.

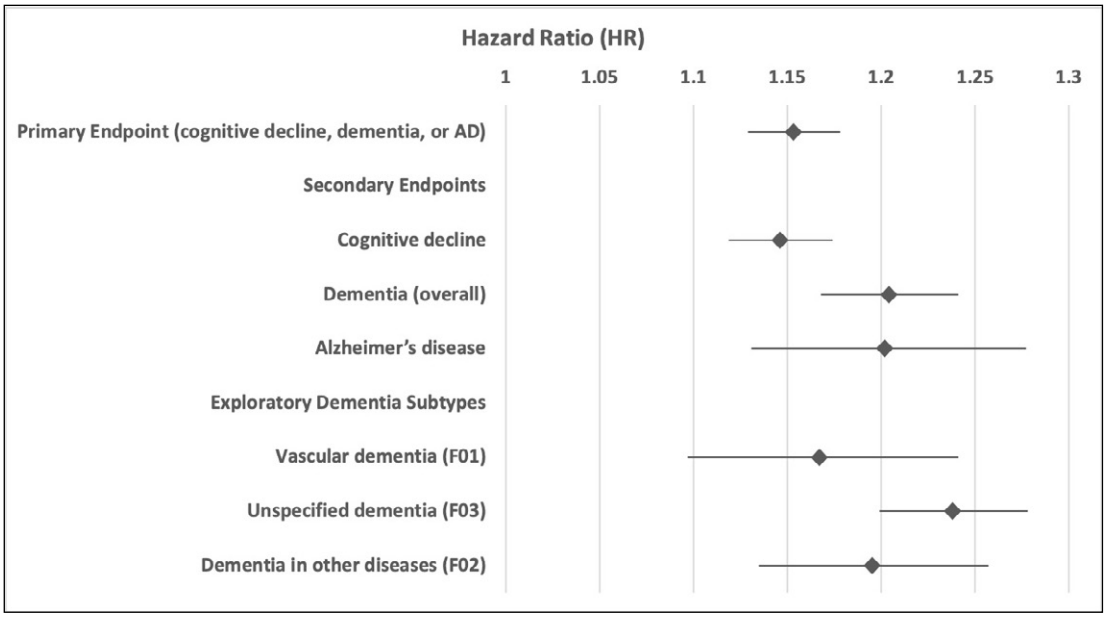

Fig. 3. Hazard ratio of the primary and secondary outcomes
Source: Own materials

However, these results contrast with earlier meta-analytic evidence by Zhuang et al. (2021) [4], which had studied the efficacy of renin–angiotensin system blockade (RASB) and the risks of cognitive decline and dementia. Their analysis showed that both ARBs and ACEIs may reduce dementia incidence, but ARBs may not confer greater benefit than ACEIs.

COGNITIVE DECLINE

The 5-year incidence of cognitive decline was higher in the ACEI cohort (24.94%) compared with the ARB cohort (22.81%). This suggests ARBs are better at maintaining global cognitive function in the long term. As expected, a network meta-analysis of 19 randomized controlled trials involving 13,734 patients demonstrated ARBs were better than ACEIs in preventing cognitive decline [10]. However, secondary analyses of three large RCTs [11, 12] did not report a distinct difference in cognitive outcomes between ACEIs and ARBs, declaring the relative cognitive advantages of these drug classes as currently inconclusive and potentially dependent on study population or study design.

DEMENTIA

Over a five-year period, the incidence of all-cause dementia was 15.63% in patients treated with ACEIs compared with 13.71% in those receiving ARBs. This difference suggests that ARBs may lower the risk of dementia relative to ACEIs. Several large cohort studies and meta-analyses have consistently reported an association between ARB therapy and a reduced incidence of dementia when compared with ACEIs [13 - 16].

Despite the consistency and biological plausibility of these findings, most of the available data come from observational studies. Direct evidence from randomized controlled trials remains limited, and therefore causality cannot be firmly established.

ALZHEIMER'S DISEASE

The 5-year incidence of Alzheimer's disease was higher in the ACEI group (4.15%) compared with the ARB group (3.51%), corresponding to a hazard ratio of 1.202 (95% CI: 1.131–1.277; $P < 0.001$). These results suggest that ARBs may provide greater protection against the development of Alzheimer's disease than ACEIs. This observation is consistent with prior studies reporting that ARBs are associated with a lower risk of Alzheimer's disease and dementia compared with ACEIs [14, 17]. The proposed mechanisms include enhanced cerebral blood flow, attenuation of neuroinflammation, and reduced amyloid-β accumulation. However, not all investigations have demonstrated this protective effect, and some studies have reported no significant differences between the two drug classes [15]. Such discrepancies may reflect differences in study design, patient populations, follow-up duration, and diagnostic criteria.

Overall, our findings add to the growing body of evidence that ARBs may offer superior neurocognitive protection compared with ACEIs in patients with HFrEF, particularly in reducing the incidence of cognitive decline, dementia, and Alzheimer's disease. Given the predominance of observational data and the limited number of head-to-head randomized controlled trials, definitive conclusions cannot yet be drawn. Future large-scale, long-term RCTs directly comparing ACEIs and ARBs with

cognitive outcomes as primary endpoints will be important to establish causality and to guide therapeutic decision-making in patients at risk of neurocognitive disorders.

STUDY LIMITATIONS

Despite the study's strengths and large real-world cohort, some limitations must be noted. New cognitive disorders were diagnosed based on diagnostic codes instead of formal cognitive tests (e.g., Mini-Cog, CogState), potentially slightly underestimating cases; however, both groups were evaluated with the same methodology, allowing for reliable comparisons to be made. HFrEF was defined by diagnostic codes rather than quantitative measurements, which could include some patients with mid-range or preserved ejection fraction, However, because the study includes a large, real-world patient population, the overall findings still likely reflect what happens in routine clinical practice, even if a few patients were misclassified. In addition, in cohorts with high mortality, as in this study, a competing-risks analysis would provide more precise estimates of absolute and relative risks for less frequent events. Due to limitations of the online analytics platform, such an analysis could not be performed. This limitation likely has minimal impact on more common outcomes, such as the primary composite endpoint and cognitive decline, but the risks for rarer outcomes, including dementia and Alzheimer's disease, may be somewhat overestimated. Furthermore, the follow-up period was short, which limited the detection of cognitive changes after the period of 3 years. Finally, as a retrospective cohort study, this analysis is inherently subject to residual confounding and selection bias despite propensity score matching. Unmeasured or unknown factors, such as socioeconomic status, lifestyle behaviors, or medication adherence, may have influenced both exposure and outcomes. Additionally, reliance on existing electronic health records limits the precision and integrity of clinical data, and causal relationships cannot be established. These limitations are inherited to observational research and should be considered when interpreting the results.

CONCLUSIONS

In this large, multicenter, propensity-matched cohort of patients with HFrEF, ACEI therapy was associated with higher 5-year rates of cognitive decline, dementia, and Alzheimer's disease compared with ARBs. ARBs demonstrated a consistent neuroprotective association across all measured cognitive endpoints, suggesting potential advantages over ACEIs in preserving cognitive function in patients with HFrEF. These findings highlight the importance of considering neurocognitive outcomes when selecting guideline-directed medical therapy for HFrEF. These observations need to be confirmed by prospective, randomized trials.

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CONFLICT OF INTEREST
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