Association between dementia and left atrial appendage occlusion in patients with atrial fibrillation: A TriNetX-based retrospective cohort study with target trial emulation

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BACKGROUND Atrial fibrillation (AF) is a common cardiac arrhythmia linked to an elevated risk of stroke and dementia. Emerging observational evidence suggests that left atrial appendage occlusion (LAAO) may reduce the risk of dementia in patients with AF; however, further research is required to confirm this potential benefit.

OBJECTIVE This study aimed to compare the effectiveness of LAAO vs direct oral anticoagulants (DOACs) in reducing the risk of dementia in patients with AF.

METHODS We conducted target trial emulation using data from the TriNetX research network. Patients with AF were allocated to 2 cohorts (2270 patients in each one), treated either with LAAO or with DOACs, and balanced with propensity score matching. The primary end points were composite dementia, vascular dementia, and Alzheimer disease. Secondary end points included mortality, ischemic stroke, intracranial hemorrhage, and major adverse cardiovascular events. Follow-up was conducted over 3 years.

RESULTS At 3-year follow-up, the risk of composite dementia was lower in the LAAO group than in the DOAC group (hazard ratio 0.57; 95% confidence interval 0.38–0.85). Subgroup analyses demonstrated consistent results, favoring the LAAO group. No significant differences were observed in the incidence of secondary outcomes.

CONCLUSION This real-world study suggests that LAAO is associated with a lower risk of dementia in patients with AF compared with DOACs. Further prospective research with long-term follow-up is needed to validate our findings in the population with AF.

KEYWORDS Left atrial appendage occlusion; Direct oral anticoagulant; Dementia; Atrial fibrillation; TriNetX

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Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting more than 59 million individuals worldwide.[1] The incidence of AF is projected to increase annually, causing a substantial rise in health burden and costs.[2,3] AF is associated with a significant proportion of cerebrovascular events, contributing to more than 20% of ischemic strokes,[4,5] leading to higher rates of disability and mortality, compared to strokes from other causes.[6,7] Moreover, recent studies have shown a significant correlation between AF and an increased risk of dementia,[8–10] independent of incident cerebrovascular events.[11] The relationship between AF and cognitive impairment may be attributed to subclinical microemboli and cerebral infarct. Evidence supports the use of oral anticoagulants not only to reduce the risk of stroke but also to prevent dementia in patients with AF.[12,13]

The 2021 American Heart Association/American Stroke Society and 2019 European Stroke Organization guidelines suggested direct oral anticoagulants (DOACs) as the preferential treatment for the prevention of thromboembolism in patients with AF.[14,15] Regarding cognitive function, numerous

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KEY FINDINGS

- Patients with atrial fibrillation (AF) who underwent left atrial appendage occlusion (LAAO) had a significantly lower risk of developing composite dementia than did those treated with direct oral anticoagulants (DOACs), with a hazard ratio of 0.57 (95% confidence interval 0.38–0.85).
- LAAO showed a trend toward reducing the risk of vascular dementia and Alzheimer disease, highlighting the need for further studies with larger cohorts or extended follow-up periods to better elucidate the effects of LAAO on specific types of dementia.
- The protective effect of LAAO in reducing dementia risk was consistent across various subgroups, including age, sex, types of atrial fibrillation, and specific types of DOACs used.

studies have demonstrated the effect of DOACs compared to warfarin[16,17] because DOAC treatments may reduce the occurrence of microthrombi, thus preventing cerebral ischemia and dementia. But despite the benefits of DOACs, there were several disadvantages, including an increased bleeding risk in susceptible patients with higher HAS-BLED scores or advanced chronic kidney diseases, which restrict their use.

On the contrary, left atrial appendage occlusion (LAAO) has emerged as a promising alternative to oral anticoagulants, showing thromboprophylaxis efficacy comparable to that of DOACs.[18] A multicenter prospective cohort study comparing the effect of LAAO and oral anticoagulants on cognition has found that LAAO is more effective in reducing cognitive decline.[19] However, current evidence comparing the effect of LAAO vs DOACs for dementia prevention in patients with AF is limited. Since these results were derived from small sample sizes and a short follow-up period, it underscores the need for further investigation into optimal treatment strategies and the assessment of long-term dementia outcomes. Therefore, we aimed to compare the effect of LAAO and DOACs on the risk of dementia in patients with AF using real-world observational data from TriNetX, a global health research network and analytics platform. Moreover, we used target trial emulation to improve causal inference.

Methods

Study design, data source, and ethical approval

We emulated a target trial in the TriNetX Global Collaborative Network, which was a global federated health research network with real-time updates of anonymized electronic medical records, comprising 126 health care organizations, around 145 million individuals from 17 countries, including academic medical centers, specialty physician practices, and community hospitals (Online Supplemental Table S1 and Online Supplemental Figure S1). As a federated research network, compliant with legal frameworks and ethical guidelines, studies using the TriNetX health research network were exempted from ethical approval and granted a waiver of informed consent, as no patient identifiable identification was received. The research reported in this article adhered to the Helsinki Declaration guidelines. Previous pharmacoepidemiological studies have used TriNetX as an important data source that has provided clinical evidence.[20,21]

Study participants

We established 2 cohorts in the TriNetX network on July 15, 2024, to investigate the occurrence of dementia in patients diagnosed with AF who were receiving LAAO or medical treatment with DOACs. The study population was drawn from the TriNetX Global Collaborative Network, encompassing the period between January 1, 2015, and June 30, 2021, following the FDA's approval of the left atrial appendage closure device in 2015. We included patients 50 years or older and with a prior AF diagnosis. The diagnosis of AF was indicated by the *International Classification of Diseases, Tenth Revision* (*ICD-10*), *Clinical Modification* codes I48.0 (paroxysmal AF), I48.1 (persistent AF), I48.2 (chronic AF), and I48.91 (unspecified AF) (Online Supplemental Table S2). We excluded patients with histories of rheumatic valvular diseases (codes I05, I08.0, I08.1, I08.3, 396, 396.8, and 396.9), prosthetic heart valve (code Z95.2), pulmonary embolism (code I26), and deep venous thrombosis (codes I82.4, I82.5, I82.6, and I82.7) as well as those who had undergone hip or knee arthroplasty procedures (Systematized Nomenclature of Medicine–Clinical Terms codes 47458005 and 19063003) or had previously used warfarin (RxNorm code 11289).

We allocated patients with AF to either LAAO or the DOAC cohort and emulated the randomization process using propensity score matching (PSM). Patients with AF who underwent percutaneous LAAO were defined using *ICD-10 Procedure Coding System* codes 02L73CK, 02L73DK, and 02L73ZK, regardless of their prior DOAC use. The DOAC group included patients with AF and newly receiving DOACs and excluded those who had previously undergone LAAO. The aforementioned treatments were identified using the corresponding *ICD-10 Procedure Coding System* code and RxNorm code (Online Supplemental Table S3). The *index date* was defined as the date when LAAO or DOAC therapy was initiated. We followed up patients from the index date until the occurrence of the outcome, death, or up to 3 years.

Outcome

The primary outcome of this study was the event rate of composite dementia within 3 years of the index date, defined using *ICD-10*, *Clinical Modification* codes F01, F02, F03, G30, and G31.83. In addition, the incidence of vascular dementia (code F01), Alzheimer disease (code G30), and unspecified dementia (code F03) was assessed separately. The secondary outcomes included all-cause mortality (deceased), ischemic stroke (code I63), intracranial hemorrhage (codes I60 and

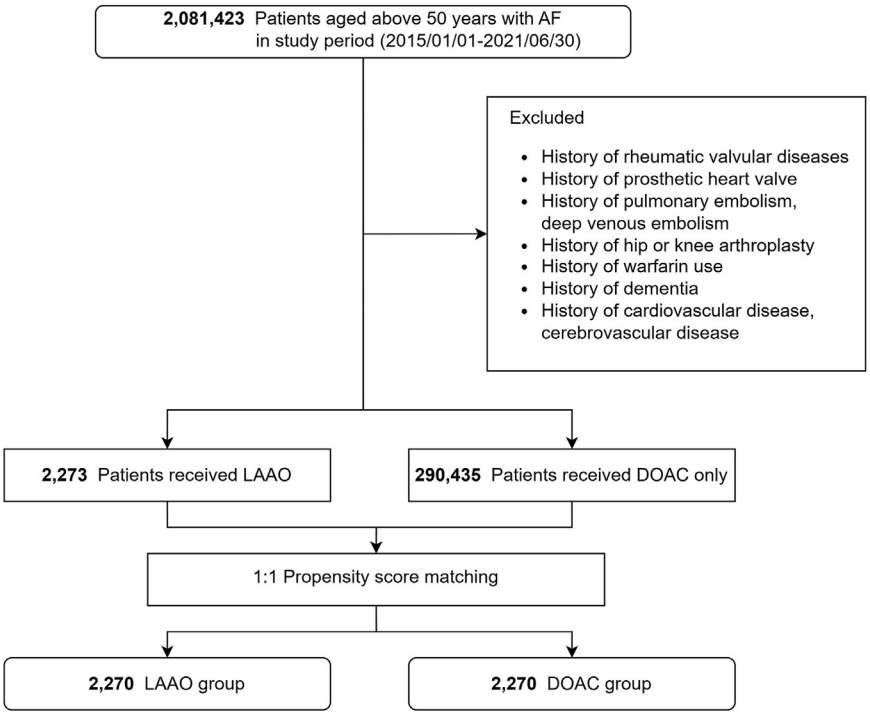

Figure 1 Flowchart for the selection of patients with AF who received LAAO and those who received DOAC only. AF = atrial fibrillation; DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion.

I61), and major adverse cardiovascular events (codes I21, I22, I60, I61, I63, and I46). Patients with prior occurrences of the outcomes of interest were excluded from the study.

Statistical analysis

All statistical analyses were performed on the TriNetX platform. Continuous variables were expressed as mean ± SD. Categorical variables were presented as frequency and percentage. PSM was implemented in a 1:1 ratio, including the following covariates: demographic characteristics (age at index date, sex, and race) and diagnoses (hypertension, diabetes, dyslipidemia, obesity, ischemic heart disease, heart failure, peripheral vascular disease, gastrointestinal hemorrhage, chronic obstructive pulmonary disease, chronic kidney disease, neoplasms, and mood disorders). Detailed codes used to identify covariates are listed in Online Supplemental Table S2. The TriNetX platform (TriNetX, LLC, Cambridge, MA) used logistic regression for PSM, using "greedy nearest-neighbor matching" with a caliper of 0.1 pooled SDs. Covariate balance was assessed using standardized mean differences (SMDs), with SMD < 0.1 indicating well-matched cohorts. Cox proportional hazards models, using R's survival package v3.2–3, were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with tests for proportionality calculated after PSM. Kaplan-Meier survival curves with log-rank tests were used to estimate survival probabilities. Subgroup analyses were performed on the basis of patient age, sex, types of AF, and types of DOAC.

Results

Patient characteristics

Our analysis within the TriNetX network delineated 2 cohorts: 2273 patients from 53 health care organizations (LAAO group) and 290,677 patients across 85 health care organizations (DOAC group) (Figure 1). Table 1 presents the baseline characteristics of these 2 groups. Before PSM, compared with patients who received DOACs, those who received LAAO were older (74 ± 6.9 years vs 70.3 ± 8.7 years) and had a higher proportion of men (61.4% vs 56.0%). Patients in the LAAO cohort also demonstrated a higher prevalence of several comorbidities than did the DOAC group, including cardiovascular diseases, dyslipidemia, gastrointestinal hemorrhage, and chronic kidney disease. After PSM, 2270 patients were included in each cohort (1:1 ratio), achieving substantial balance (SMD < 0.1) across variables.

Risk of dementia

During the follow-up period of 3 years, 36 patients in the LAAO group (1.6%) and 68 patients in the DOAC group (3.0%) experienced an event of composite dementia (Table 2). Patients receiving LAAO were associated with a reduced risk of composite dementia (HR 0.57; 95% CI 0.38–0.85) (Figure 2).

In the analysis of specific dementia types, no significant differences were observed between the 2 cohorts in vascular dementia (HR 0.51; 95% CI 0.19–1.33), Alzheimer disease (HR 0.54; 95% CI 0.25–1.16), or unspecified dementia (HR 0.71; 95% CI 0.44–1.15) (Online Supplemental Figures S2 and S3).

Table 1 Baseline characteristics of LAAO- and DOAC-treated patients before and after propensity score matching

Characteristic	Before propensity score matching			After propensity score matching		
	LAAO (n = 2273)	DOAC (n = 289,659)	SMD	LAAO (n = 2270)	DOAC (n = 2270)	SMD
Demographic characteristics						
Age (y)	74.0 ± 6.9	70.3 ± 8.7	0.46	73.9 (6.9)	74.1 (7.0)	0.02
Male	1395 (61.4)	162,151 (56.0)	0.11	1392 (61.3)	1405 (61.9)	0.01
White	1585 (69.7)	217,238 (75.0)	0.12	1584 (69.8)	1557 (68.6)	0.03
Comorbidities						
Hypertension	1063 (46.8)	103,729 (35.8)	0.22	1061 (46.7)	1053 (46.4)	0.01
Chronic ischemic heart disease	651 (28.6)	41,551 (14.3)	0.35	648 (28.5)	637 (28.1)	0.01
Heart failure	443 (19.5)	32,954 (11.4)	0.23	441 (19.4)	396 (17.4)	0.05
Peripheral vascular disease	115 (5.1)	7,024 (2.4)	0.14	115 (5.1)	92 (4.1)	0.05
Dyslipidemia	579 (25.5)	56,622 (19.5)	0.14	579 (25.5)	535 (23.6)	0.05
Diabetes mellitus	365 (16.1)	44,353 (15.3)	0.02	365 (16.1)	353 (15.6)	0.01
Overweight and obesity	257 (11.3)	29,606 (10.2)	0.04	256 (11.3)	234 (10.3)	0.03
Chronic kidney disease	251 (11.0)	22,352 (7.7)	0.11	251 (11.1)	235 (10.4)	0.02
Chronic obstructive pulmonary disease	193 (8.5)	19,431 (6.7)	0.07	193 (8.5)	160 (7.0)	0.05
Neoplasms	312 (13.7)	38,485 (13.3)	0.01	312 (13.7)	299 (13.2)	0.02
Mood disorders	128 (5.6)	16,707 (5.8)	0.01	128 (5.6)	104 (4.6)	0.05
Gastrointestinal hemorrhage	262 (11.5)	2,077 (0.7)	0.46	259 (11.4)	251 (11.1)	0.01

Values are presented as mean ± SD or n (%).
DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion; SMD = standardized mean difference.

Secondary outcomes

At 3-year follow-up, the risk of all-cause mortality, major adverse cardiovascular events, ischemic stroke, and intracranial hemorrhage are comparable between the LAAO group and the DOAC group (Table 3). The Kaplan-Meier curves for these outcomes are presented in Online Supplemental Figures S4–S7.

Subgroup analyses

In subgroup analyses, the LAAO group consistently displayed trends of a reduced risk of composite dementia compared with the DOAC group, irrespective of age (≥80 years: HR 0.73, 95% CI 0.44–1.22; 50–79 years: HR 0.64, 95% CI 0.25–1.65), sex (male: HR 0.56, 95% CI 0.30–1.02; female: HR 0.61, 95% CI 0.33–1.13), types of AF (paroxysmal AF: HR 0.66, 95% CI 0.40–1.09; persistent AF: HR 0.88, 95% CI 0.46–1.70; chronic AF: HR 0.35, 95% CI 0.16–1.74), types of DOAC (dabigatran: HR 0.32, 95% CI 0.16–0.64; apixaban: HR 0.59, 95% CI 0.37–0.93; rivaroxaban: HR 0.66, 95% CI 0.42–1.03; edoxaban: HR 0.43, 95% CI 0.21–0.86) (Figure 3).

Discussion

In this study, we used the real-world observational data from TriNetX, comprising 2 large cohorts of patients across multiple health care organizations worldwide, to compare the effect of LAAO vs DOACs on dementia risk in patients with AF. We observed a reduced risk of composite dementia in patients receiving LAAO group compared with those receiving DOACs. The noninferiority of LAAO compared with DOACs in reducing the risk of cardiovascular events, cerebrovascular events and all-cause mortality, as observed in previous studies,[18,22,23] further strengthens our findings.

AF is increasingly acknowledged as an independent risk factor for incident dementia and worsening of preexisting cognitive impairment, regardless of stroke history.[11,24] The

Table 2 Primary outcomes among included patients in each cohort

Study outcome	Original population			Propensity score–matched cohort		
	Patients in the cohort, n	Patients with outcomes, n (%)	HR (95% CI)	Patients in the cohort, n	Patients with outcomes, n (%)	HR (95% CI)
Composite dementia						
LAAO	2,273	36 (1.6)	0.83 (0.60–1.16)	2270	36 (1.6)	0.57 (0.38–0.85)
DOAC	290,435	6030 (2.1)	1.00 (reference)	2270	68 (3.0)	1.00 (reference)
Vascular dementia						
LAAO	2273	10 (0.4)	0.81 (0.36–1.80)	2270	10 (0.4)	0.51 (0.19–1.33)
DOAC	290,435	1039 (0.4)	1.00 (reference)	2270	13 (0.6)	1.00 (reference)
Alzheimer disease						
LAAO	2273	10 (0.4)	0.91 (0.49–1.70)	2270	10 (0.4)	0.54 (0.25–1.16)
DOAC	290,435	1530 (0.5)	1.00 (reference)	2270	20 (0.9)	1.00 (reference)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; LAAO = left atrial appendage occlusion.

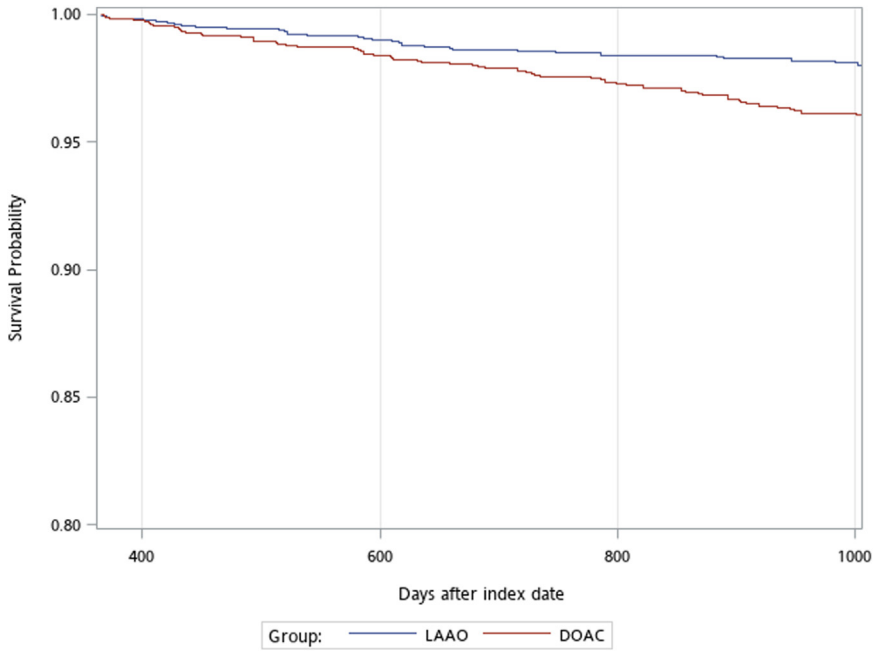

Figure 2 Kaplan-Meier curves showing survival free from composite dementia in the LAAO-treated group (*blue*) compared with the DOAC-treated group (*red*). $P < .01$. DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion.

correlation between AF and cognitive decline is partly attributed to mechanisms such as silent cerebral infarctions and reduced brain volume.[25,26] Patients with AF exhibit a higher prevalence of silent cerebral infarctions and brain atrophy, particularly in those with a higher AF burden, including persistent AF and longer disease duration.[27] Considering the relationship between AF and dementia, as well as the significant health burden associated with both conditions, the treatment and management of AF are important.

In our original population, LAAO showed no significant difference in dementia risk compared with DOACs, while after PSM, LAAO was associated with a lower risk of dementia. We observed that the LAAO group had more cardiovascular diseases and vascular risk factors, potentially contributing to vascular cognitive decline. Once covariates were balanced after PSM, the protective effect of LAAO became evident, demonstrating a greater reduction in dementia risk compared to DOACs. Currently, evidence directly comparing the effect of LAAO vs DOACs on dementia is limited, with most studies focusing on the effectiveness of these treatments in preventing stroke and other cardiovascular events. A prospective cohort study by Mohanty et al[19] compared the effect of LAAO vs oral anticoagulants on change in Montreal Cognitive Assessment score over a 1-year follow-up period in patients with AF after ablation. The study found a substantial decline in cognitive function in patients who remained on oral anticoagulants, significantly different from the LAAO population,[19] highlighting the

Table 3 Secondary outcomes among included patients in each cohort

	Original population			Propensity score–matched cohort		
Study outcome	Patients in the cohort, n	Patients with outcomes, n (%)	HR (95% CI)	Patients in the cohort, n	Patients with outcomes, n (%)	HR (95% CI)
All-cause mortality						
LAAO	2273	151 (6.6)	1.39 (1.18–1.63)	2270	151 (6.7)	1.16 (0.93–1.47)
DOAC	290,435	15,320 (5.3)	1.00 (reference)	2270	141 (6.2)	1.00 (reference)
MACE						
LAAO	2273	131 (5.8)	1.17 (0.99–1.39)	2270	129 (5.7)	1.01 (0.80–1.29)
DOAC	290,435	15,731 (5.4)	1.00 (reference)	2270	138 (6.1)	1.00 (reference)
Ischemic stroke						
LAAO	2273	75 (3.3)	1.34 (1.07–1.68)	2270	75 (3.3)	1.08 (0.78–1.49)
DOAC	290,435	7828 (2.7)	1.00 (reference)	2270	75 (3.3)	1.00 (reference)
Intracranial hemorrhage						
LAAO	2273	10 (0.4)	1.18 (0.63–2.20)	2270	10 (0.4)	1.10 (0.46–2.63)
DOAC	290,435	1187 (0.4)	1.00 (reference)	2270	10 (0.4)	1.00 (reference)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; LAAO = left atrial appendage occlusion; MACE = major adverse cardiovascular event.

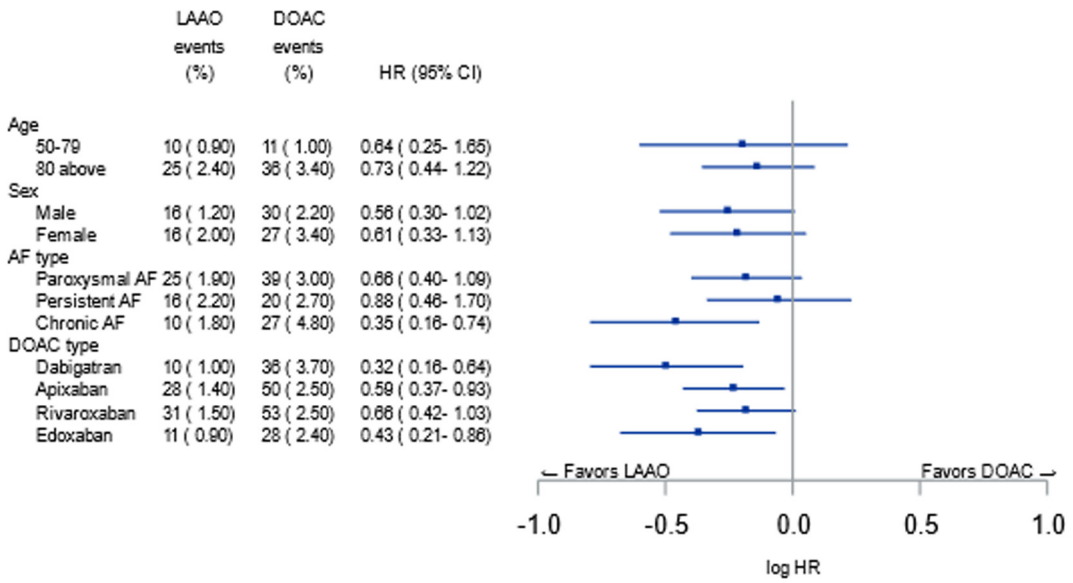

Figure 3 Subgroup analyses of composite dementia for the LAAO group and DOAC group. AF = atrial fibrillation; CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; LAAO = left atrial appendage occlusion.

superior efficacy of LAAO in preventing cognitive decline, which aligns with our findings. However, our analysis did not reveal significant differences between the LAAO and DOAC groups with regard to the incidence of vascular dementia, Alzheimer disease, and unspecified dementia. This lack of differentiation could be due to multifactorial pathophysiology of dementia, involving vascular, neurodegenerative, and neuroinflammatory processes.[28–31] These complexities contribute to the clinical challenges in achieving accurate dementia classification.[32] Despite this, there was a nonsignificant trend toward protective effects in individual dementia types, suggesting potential benefits that might become more evident with larger sample sizes or longer follow-up periods. Further pharmacoepidemiological studies may be needed to explore the effect of LAAO on specific types of dementia in more depth, using the multinational collaborative research network.[33]

The possible explanation for the reduced dementia risk may involve several aspects. First, LAAO, by effectively sealing off the left atrial appendage, could diminish the formation of microemboli and cerebral thrombosis,[22,34] consequently reducing the incidence of cerebral infarcts and the resulting cognitive impairment. Second, LAAO demonstrates more stable efficacy in thrombophylaxis than do DOACs. The efficacy of DOACs is limited by suboptimal anticoagulation due to noncompliance or underdosing[35] and fluctuating plasmatic concentrations, influenced by renal function and drug-drug interactions.[36,37] Third, the risk of cognitive decline may be exacerbated by cerebral microbleeds,[38–40] often a consequence of prolonged anticoagulation.[41,42] Further research is warranted for serial neuroimaging follow-up to compare the burden of silent microbleeds between patients treated with LAAO and those treated with DOACs.

The current guideline recommends LAAO for stroke prevention in patients with AF who have contraindications for long-term anticoagulant treatment,[43] considering the advantage of LAAO in reducing the incidence of hemorrhagic stroke compared to oral anticoagulants, as demonstrated in previous studies.[44] However, our findings show no significant difference in intracerebral hemorrhage between patients treated with DOACs and those treated with LAAO. This discrepancy may be explained by the clinical consideration that the LAAO group often includes patients who are unsuitable for or intolerant of DOACs and have more complex comorbidities, making them inherently at a higher risk of intracerebral hemorrhage.

Our research stands out for its inclusion of a large cohort and an extensive follow-up period, strengthened by target trial emulation to improve causal inference. Moreover, we used PSM to mimic the randomization between groups. However, we acknowledge several limitations to this study. First, the reliance on electronic medical records from health care organizations and *ICD-10* codes for study population inclusion raises the possibility of misclassification and underreporting of dementia events. Nonetheless, such a potential of misclassification should occur nondifferentially between the LAAO and DOAC cohorts. Second, the lack of cognitive function testing in this study limits our ability to measure cognitive changes, which may be more functionally relevant. Future prospective study would be necessary to validate the results of our study. Third, this study may be subject to potential immortal time bias, as patients receiving LAAO may take DOACs during the waiting time period before that procedure. However, we observed no difference in all-cause mortality between the LAAO and DOAC groups, indicating that this bias may not substantially affect our results. In addition, the observed noninferiority in cerebrovascular and cardiovascular events between the 2 cohorts further strengthens our findings, thereby minimizing concerns regarding such bias. Fourth, in clinical practice, some patients may continue

short-term or long-term antiplatelet or oral anticoagulation therapy after LAAO, depending on the type of device implanted, the risk of thromboembolism, and their cardiovascular comorbidities. This may underestimate the protective effect of LAAO on dementia. Future research is warranted to clarify the specific role of these therapies in relation to dementia risk after LAAO. Finally, although some residual confounding factors such as lifestyle variables were unable to be captured in the database, we have applied the target trial emulation and performed PSM to balance baseline characteristics between the 2 cohorts. In addition, the cardiovascular outcomes align with previous studies, suggesting that these residual confounding factors may not have a substantial effect on our results.

Conclusion

In our emulated trial using the TriNetX network, we observed that patients who underwent LAAO exhibited a lower incidence of dementia than did those receiving DOACs. The similarity in the effects of cardiovascular events, cerebrovascular events and all-cause mortality between groups, consistent with previous studies, further strengthens our findings. Further studies are warranted to evaluate the effect of LAAO vs oral anticoagulation on cognitive function and different types of dementia and to determine the population most likely to benefit from treatments aimed at halting cognitive decline.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used GPT-4 in order to improve the readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: This study was granted a waiver of informed consent, as patient information was de-identified.

Ethics Statement: Studies using the TriNetX health research network were exempted from ethical approval; the research reported in this article adhered to the Helsinki Declaration guidelines.

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